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American Heart Journal

VOL. 51 MAY, 1956 No. 5

Original Communications

THE INFLUENCE OF THE INVESTIGATIONS OF HELMHOLTZ ON ELECTROCARDIOGRAPHY

DEMETRIO SODI-PALLARES, M.D.

MEXICO, D.F.

HERMANN Ludwig Ferdinand von Helmholtz was born on the 31st of August, 1821, in Potsdam,[1] near Berlin. He died on the 8th of September, 1894, seven years before Willem Einthoven completed his string galvanometer on which he worked for several years. The construction of this apparatus signaled the beginning of clinical electrocardiography. It is difficult to conceive how this German philosopher could have carried out investigations that continue to be of more and more importance in the field of present day electrocardiography.

Helmholtz' studies on the physiology of the eye and optics, as well as the physiology of the ear and acoustics, his measurements of the velocity of the nerve impulse,[2] in 1850, and his invention of the ophthalmoscope[1] in 1851, are well-known facts. "Perhaps his greatest contribution, however, was his attempt to account for our perception of quality of tone. He showed, both by analysis and by synthesis, that quality depends on the order, number, and intensity of the overtones or harmonics that may, and usually do, enter into the structure of a musical tone. He also developed the theory of differential and of summational tones. His work on sensations of tone (1862) may well be termed the principia of physiological acoustics. He may also be said to be the founder of the fixed-pitch theory of vowel tones, according to which it is asserted that the pitch of a vowel depends on the resonance of the mouth, according to the form of the cavity while singing it, and this independently of the pitch of the note on which the vowel is sung."[1]

If his contributions to medicine are of great importance, I would like to point out that his contributions to physics are of still greater importance. One of the most commonly known physical discoveries is the first law of thermodynamics, or the law of the conservation of energy.

From the Instituto Nacional de Cardiología, México, D. F.
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The studies of Benjamin Thompson[1] (Count Rumford) led to the conclusion, in 1840, that heat was not a material substance, since he observed that an isolated body could produce unlimited heat. However, his concepts were not accepted by the scientists of his day.

Two years later Robert Mayer[1] presented a paper which passed unnoticed by the physicists of his time. It contained facts which led him to the conclusion that all work is transformed into heat. He found that all work necessary to compress air was converted into heat.

In 1844 and 1845, Dr. James Prescott Joule[1] continued the studies of Mayer on the compression and expansion of air, and after detailed investigations, he established the mechanical equivalent of heat. Therefore, his studies occupy the place of honor among those leading to the law of the conservation of energy. In many of his experiments he collaborated with W. Thomson, the famous Lord Kelvin.

These earlier works allowed Helmholtz to publish, in 1847, his classic paper on "The Conservation of Energy." From the theoretical viewpoint, this paper constituted the strongest support that finally led to the conclusion that the energy of the universe is constant.*

It is not possible in this paper to go into more detail concerning the discoveries of Helmholtz in the fields of hydrodynamics, electrodynamics, and theories of electricity, meteorological physics, electrical oscillations, and general mathematical terms applied to closed circuits, into his formulas applicable to the velocity of the propagation of electromagnetic induction, his studies on electrical and magnetic polarization, and the phenomena of electrolysis, and his ideas which led his pupil Hertz to the demonstration of the existence of electromagnetic waves.

We will take a look at those investigations of Helmholtz which influenced the study of the electrical phenomena of the heart and see if they were, as I mentioned, of such importance.

Three of Helmholtz's principles[3] have tremendous importance in modern electrocardiography. These are, in their order of importance:

1. The principle of superposition.
2. The principle of reciprocity.
3. The principle of the electromotive surface, or of the double membrane.

At 32 years of age, Helmholtz[3] showed great interest in the bio-electrical investigations carried out by Emil du Bois Reymond. In 1853 he studied the distribution of electrical currents in volume conductors and demonstrated the three theorems mentioned above. Recently Frank N. Wilson and Robert H. Bayley[3] have made important studies on the same subject.

Let us now review each of these three theorems separately.

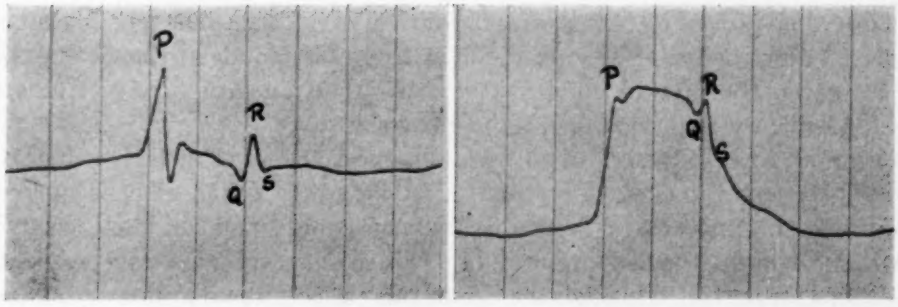
1. *The Principle of Superposition.*—This theorem can be defined in the following manner[3]: "Let there be given a system of conductors within which electromotive forces are arbitrarily distributed. The currents and the potential

*"The general equation of thermodynamics consistent with the above investigations may be written: Heat entering a system = Increase of energy of the system plus the external work done by the system during the entry. It is clear from this that it is erroneous to speak of the heat in a body."[1]

differences due to all these electromotive forces acting together are the same as those obtained by adding algebraically all the currents and potential differences that would be produced by the individual electromotive forces, each acting independently."

This principle is applied to the electric forces generated by the heart. For example, if the auricular and ventricular activity occur simultaneously, the tracing will show deflections which correspond to the algebraic sum of the auricular and ventricular phenomena.

In Fig. 1,*B*, it can be observed that the ventricular complex is superimposed on a monophasic auricular wave. The first part of Q, as well as the final part of S, is very far from the base line and the level of inscription of the different waves of the ventricular complex has been altered. The morphology of QRS has become modified in accordance with the principle of superposition: the ventricular activity is superimposed to an auricular phenomenon which gradually decreases.



A. *B.*

Fig. 1.

In the control (Fig. 1,*A*) the ventricular complex is of the QRS type, and when this complex is superimposed onto the monphasic auricular wave (Fig. 1,*B*), then the positive deflection diminishes considerably in voltage and the S is deeper and of greater voltage than the R.

We know now that before we were acquainted with this principle, many of our comments were based upon it. For example, we attempted to explain why the R waves of V_5 and V_6 in complete left bundle branch block have a smaller voltage than the same deflection in incomplete B.B.B. and in normal tracings. When L.B.B.B. is complete, there is a powerful septal force which points from right to left and determines the positivity of V_5 and V_6; in spite of this the voltage of R is less in these leads if compared with the control when this septal force does not exist. In the control the voltage of R is fundamentally due to the forces which correspond to the electrical activity of the free wall of the left ventricle. These forces are not changed when the B.B.B. is complete and, furthermore, the already mentioned septal forces will tend to increase the voltage of R. Why then does the voltage of the positive deflection decrease?

Analysis of the curves and the principle of superposition give us the explanation. Registration of the electrical forces which correspond to the free wall occur at the moment in which the intrinsic deflection of the septal forces is inscribed. This

reasoning is true mainly for the inferior portions of the free wall and interventricular septum. Now in V_5 and V_6 which explore, fundamentally, the lower ventricular regions, there are two opposite and antagonistic forces: The intrinsic deflection of the septal forces, which tends to give negativity, and the forces of the free left ventricular wall which give positivity. On the magnitude and rapidity of inscription of these forces depends the voltage of the R wave in the left precordial leads.

2. *The Principle of Reciprocity.*—This theorem is valid for any homogeneous or heterogeneous volume conductor.[3] In regard to the heart the principle can be stated in the following manner: If a current i of given magnitude flows between elements a and b of the cardiac muscle, the resulting difference of potential registered between any two electrodes placed on the body surface will be equal to the difference of potential between the elements a and b when a current i of equal magnitude is applied between the two electrodes on the body surface.[3]

Recently, McFee and collaborators[4] have demonstrated a new method for recognizing the value of electrocardiographic leads. This is based on Helmholtz's principle of reciprocity. They studied, in hydraulic models, the flow of fluids which resemble the flow of electric currents. The lines of flow of fluids used are made visible by the use of special coloring solutions.

Wilson and associates[5] studied, through the suggestion of Kenneth S. Cole, the principle of reciprocity. For this study they applied an electric current to two electrodes on any two of the three limbs and could determine on the surface of the human body the isopotential line which corresponded to the electrode of the other extremity. Through the use of this procedure an approximate idea of the electrical properties and the distribution of the electric currents in the human body are obtained. Various authors, on the other hand, are studying the characteristics of the different types of leads based on the same principle. Lepeschkin,[6] applying the same theorem, proposed the method of "curvilinear squares" and defines the "tubes of flow" which are of variable sizes but of equal resistence, each one with the same fraction of the total current.

Lepeschkin, by means of a theoretic analysis, has made it possible to understand the distribution of the flow tubes which are denominated "tubes of influence" of a lead.[6] Understanding the distribution of the "tubes of flow" for any lead, it is possible to infer, through the shape and voltage of the ECG obtained in that lead, the possible locations of the polarized surfaces in the heart muscle.

McFee and Johnston[7] also recently applied the principle of reciprocity and they arrived at the following fundamental theorem which defined the relations between a lead and the electromotive forces of the heart:

> "The open circuit voltage (v) produced in any lead is related to the electromotive forces of the heart by the equation
>
> $$v = e_1 i_1 + e_2 i_2 + \ldots\ldots$$
>
> where the e's are the potential differences of the electromotive force elements, and the i's are the currents passing through the elements when a unit current is introduced into the lead."

These same authors[7] analyze the leads as vectors, on applying to them unitary currents. From this is derived a current of flow which has a certain intensity and direction in each point of the human body. In other words, the current of flow forms a "vectorial field." The magnitude and direction of the current flow in any point can be represented by a symbol $\vec{J}$. The authors succeed in transforming the previous equation in order to obtain the following:

$$v = J_1 \cdot e + J \cdot e + \ldots .$$

"This means that the current field ($\vec{J}$), at a point in the heart resulting from the introduction of a unit current into the lead, has the same direction and intensity as the Burger lead vector of that lead with respect to electromotive forces located at that point."

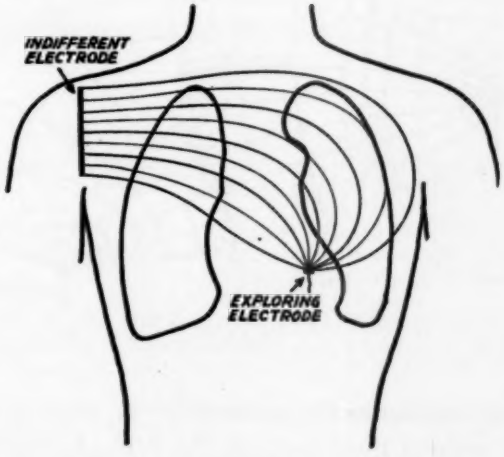


Fig. 2.

In a unipolar lead the meaning of the exploring and indifferent electrodes has been defined in terms of lines of flow.

When a unit current is applied to the electrodes of a unipolar lead, a vectorial field is produced. The lines of current seem to radiate from the exploring electrode and the density of the current at any point considered in the body diminishes in proportion to 4π times the distance from that point to the exploring electrode.[7] This shows that the current density and the concentration of the flow lines greatly decrease at the distant electrode; there, the lines of flow tend to become parallel (Fig. 2).

In a bipolar lead with the two electrodes in contact or close to the heart, the lines of flow radiate from both electrodes (Fig. 3).

3. *The Principle of the Electromotive Surface.—*

I believe that this principle is of the utmost importance and has great application in our present day knowledge of electrocardiography. We will see, once it is defined, how it applies to the heart and human body.

For any conductor (heart) in the interior of which electromotive forces are found distributed arbitrarily (cardiac dipoles or activation waves), there is a double layer located on the surface of the conductor (potential variations on the epicardial surface of the heart) which will determine in a second conductor (tissues which surround the heart and which form a volume conductor) placed in contact with the first, the same currents and differences of potential (as shown by our close or distant leads) which would have been produced by the electromotive forces (activation waves) of the first conductor (heart) acting alone under the same circumstances.

It is sufficient to study Helmholtz's demonstration of his theorem[3] in order to accept as equivalents the double layer located on the surface of the first conductor with the variations or differences of potential on its same surface.

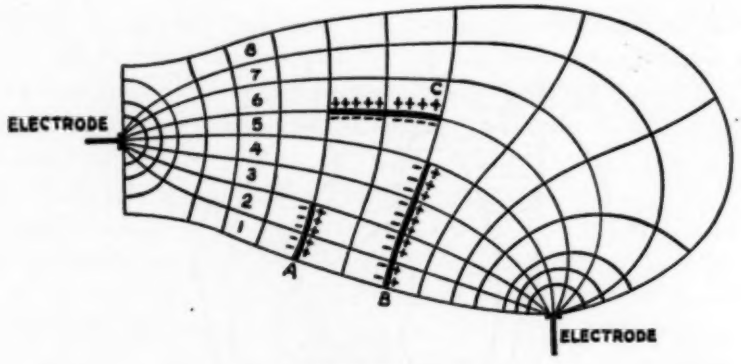


Fig. 3.

This theorem does not define the potential of a point on the second conductor in relation with the surface potentials of the first; I believe that this work of Helmholtz's was that which inspired Wilson to apply Poisson's integral to these problems[8] and to define the potential of any point on the second conductor as a function of the potential of each one of the elements on the surface of the first conductor.

When we use the term "potential" we do not refer to electromotive force as is often thought and as it is often used in pure physiologic research, but it denotes the concept which is employed in electricity and which was defined by Green and by Gauss.[9] That is, we do not speak of "action potential" but of "Gaussian potential."[9]

With Wilson's analysis it is easy to demonstrate, especially in the precordial leads, that the potential variations in the precordial electrodes are similar to the potential variations from the subjacent epicardial regions proximal to the electrode. This occurs, preferably, when the surface variations are the same, or nearly the same, in extensive epicardial zones or areas. This means that the morphology of the epicardial tracings is very similar to the morphology of the precordial tracings. The theoretic analysis would have little value if it were not completed by studies carried out in man and animals, which have demonstrated the great similarity already mentioned.

The knowledge of the morphology of the unipolar tracings in normal and pathologic conditions is indispensable for the understanding and realization of a correct electrocardiographic interpretation.

I believe that we have clearly demonstrated the enormous influence of Helmholtz's investigations on modern electrocardiography.

SUMMARIO IN INTERLINGUA

Ben que von Helmholtz moriva in 1894, septe annos ante que Einthoven completava su galvanometro a corda e assi marcava le comenciamento del electrocardiographia clinic, certe principios establite per von Helmholtz in 1853 como fructos de su interesse in investigationes bio-electric remane de importantia fundamental in le electrocardiographia de nostre dies. Isté principios es: (1) Le principio del superposition. (2) Le principio de reciprocitate. E (3) le principio del superficie electromotive o del membrana duple.—Le signification perdurative de iste principios es demonstrate in detalio.

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THE QRS COMPLEX OF THE ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION WITH REMARKS ON METHODS OF RECORDING. II *

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APICAL MYOCARDIAL INFARCTION

FIG. 1 depicts the effect of an apical infarction upon the waves of excitation, the spatial QRS loop, and the limb leads of the electrocardiogram. The first portion of the loop is shortened as a result of apical infarction, and is swung posteriorly. The frontal plane loop assumes a figure-of-eight configuration and is much narrower than the normal loop. The longer duration of the initial portion of the loop increases the duration of the Q in Lead I with only slight, if any increase in its depth. The shortening of the 0.04 second vector results in a decrease in the amplitude of the R in Lead I. The direction of the vectors at 0.015 through 0.025 second are such that there is a decrease in the R and the appearance of an early S wave in Lead II. The configuration and timing of the first portion of the apical infarction loop results in a decrease in the amplitude and increase in the duration of the R in Lead III, and a narrowing of the S wave in Lead III.

The precordial leads in the presence of an apical infarction (Fig. 2) show a wide Q in V_4 and V_5.

Fig. 3 is an illustrative set of electrocardiograms from a patient with an apical wall infarction whose heart is in the same electrocardiographic position and rotation as that of the basic diagrams.

Fig. 4 shows the normal and infarct loops in their proper relation to one another for various degrees of rotation on the three axes. With the loop counterclockwise (Fig. 4,*a*) there is an increase in the duration of the Q in Leads I, II, and V_L. With the loop clockwise (Fig. 4,*b*) there is an increase in the duration of the Q in Leads II, III, and V_F, and a small M- or W-shaped QRS configuration in Lead I. With an apex back, intermediate, counterclockwise heart position (Fig. 4,*e*) a W-shaped complex appears in Lead I and the normal Q in V_R is markedly decreased in amplitude.

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*This is a continuation of an article under the same title which appeared in the April issue of this JOURNAL 51:501, 1956.

INFARCTS IN COMBINED LOCATIONS

The majority of infarcts are not confined to the distributions presented in the preceding basic diagrams, but are found in combinations of such locations. Fig. 5 is a diagram of the left ventricle showing various common areas of infarction; *A*, *B*, *C*, *D*, *E*, and *F*. The numbered loops *1* to *9* show the normal and infarct loops for infarction in combinations of these areas. For the most part each area has its effect. However, the presence of septal infarction does not always have the same simple effect, for the infarct may be largely leftsided, or transmural.

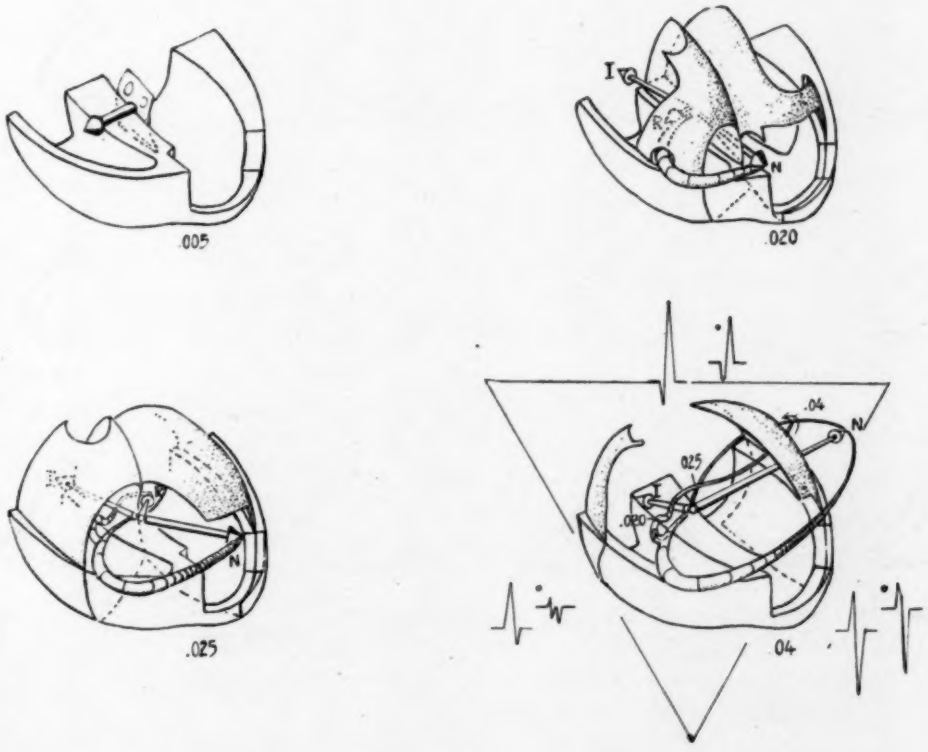


Fig. 1.—The same method is employed for analysis of the effect of apical infarction as shown for infarcts in other locations. Special attention is drawn to the timing of the infarct loop.

A study of the various loops of Fig. 5 shows how infarction in various combined locations may result in frontal plane loops and, therefore, limb leads which are quite similar, even in timing, to loops produced by infarction in other locations. Compare Fig. 5,*1* and *3*. The spatial loops are, as indicated, different since in Fig. 5,*3* the ascending limb of the loop dips down and backward.

Fig. 5,*a*, represents the loops before and after infarction in a patient whose transverse apex back, counterclockwise heart sustained an infarction in areas *E*, *A*, and *B*. The electrocardiograms are shown in Fig. 6.

RÉSUMÉ

The detailed analysis of the loops in myocardial infarction as presented on a hypothetical physiologic basis, in so far as we know, has not been attempted before. Grishman's observations[2] and conclusions, to the extent to which they deal with infarction loops, are in general agreement.

In general the analysis of the QRS loops in myocardial infarction described above has proved very accurate when checked by study of autopsied cases. Where no previous tracing is available the diagnosis of infarction and the prediction of the location of the infarct from the postinfarction tracings alone is

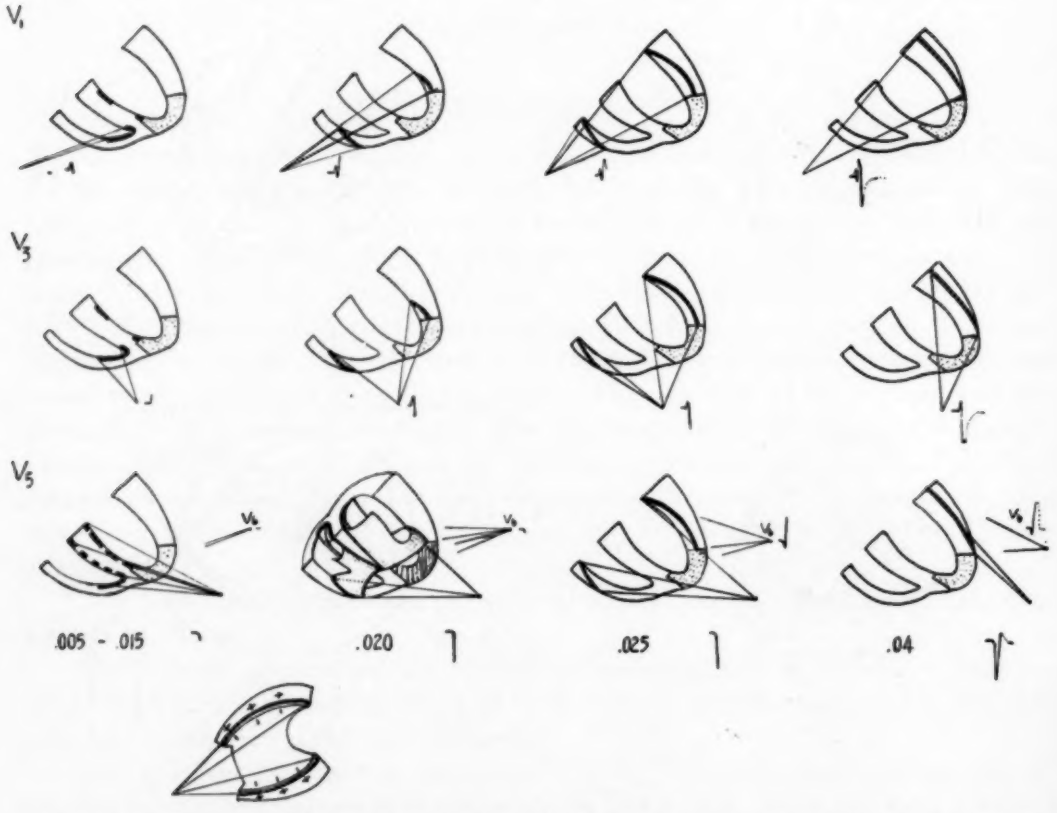
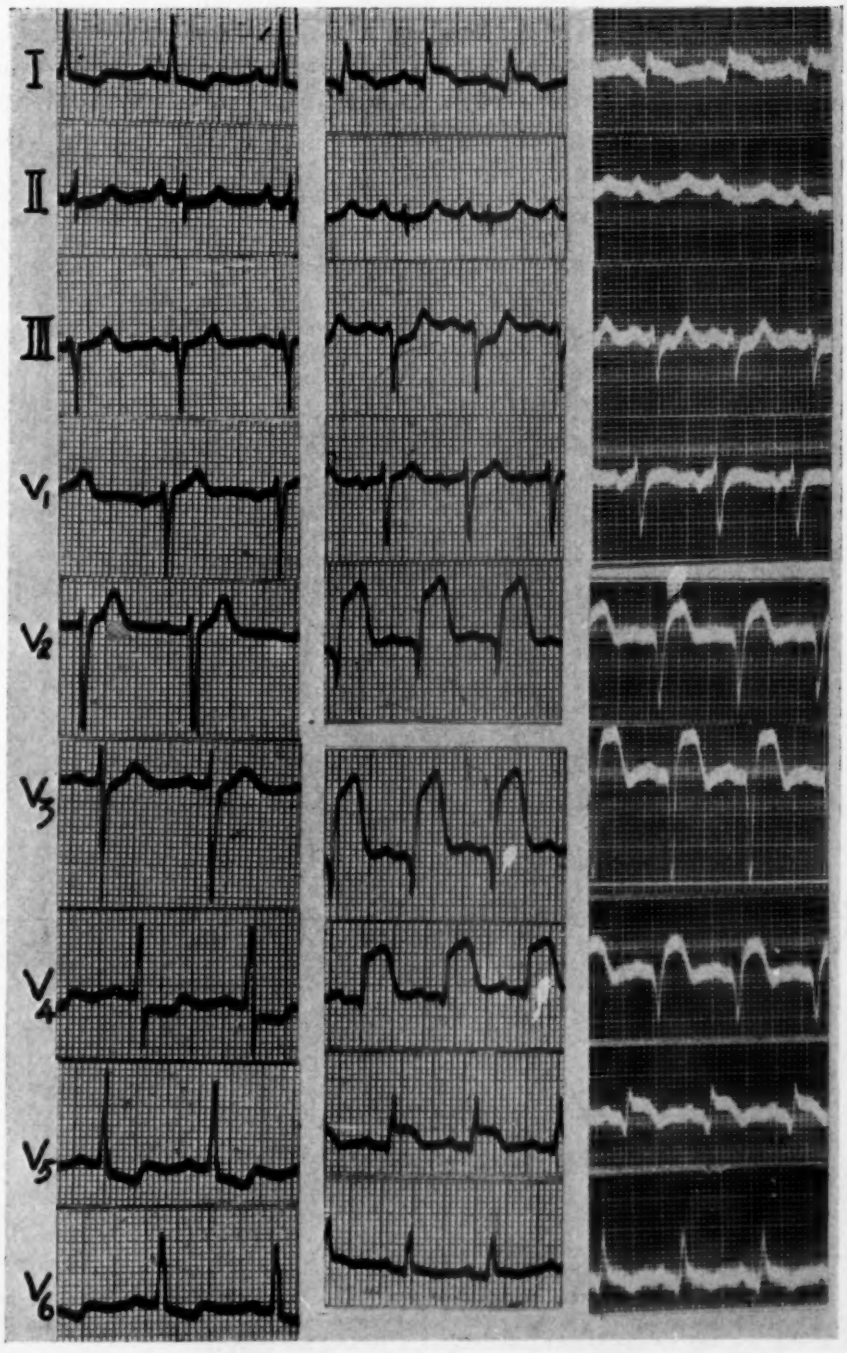


Fig. 2.—The same method is employed for the analysis of the effect of apical infarction as was utilized for infarcts in other locations.

The 0.020 second diagram for V_5 is drawn in three dimensions and, while solid angles to all the waves of excitation are not drawn, they can perhaps be visualized with the aid of the longitudinal diagram of the left ventricle below the figure. That the electrode faces a good deal of negative surface and little positive surface is evident.

less accurate. However, application of the approach presented here has led to more accurate appraisal of such tracings than can be accomplished by more empirical methods. Finally, the recognition of the impossibility of distinguishing the normal from the pathologic in some cases has made it possible to avoid false conclusions resulting from the employment of erroneous methods purporting to make such distinction. This is especially true of tracings which are compatible with the presence of diaphragmatic and of septal infarction. When it is also



A. *B.*

Fig. 3.—This figure shows electrocardiograms before (*A*) and after (*B*) infarction of the apical portion of the left ventricle of a patient whose heart was in approximately the position and rotation shown in Fig. 1. The infarct extended a bit more into the lateral wall than shown in Fig. 1, causing the loop to shorten more. The close correspondence of both the limb leads and the precordial leads to those shown in Figs. 1 and 2 is evident.

realized that, as a result of the taking of food, T-wave changes can occur which simulate those occurring in diaphragmatic infarction, the importance of serial electrocardiograms will be more generally appreciated. It is important to be aware of changes in QRS configuration which can occur normally in the same

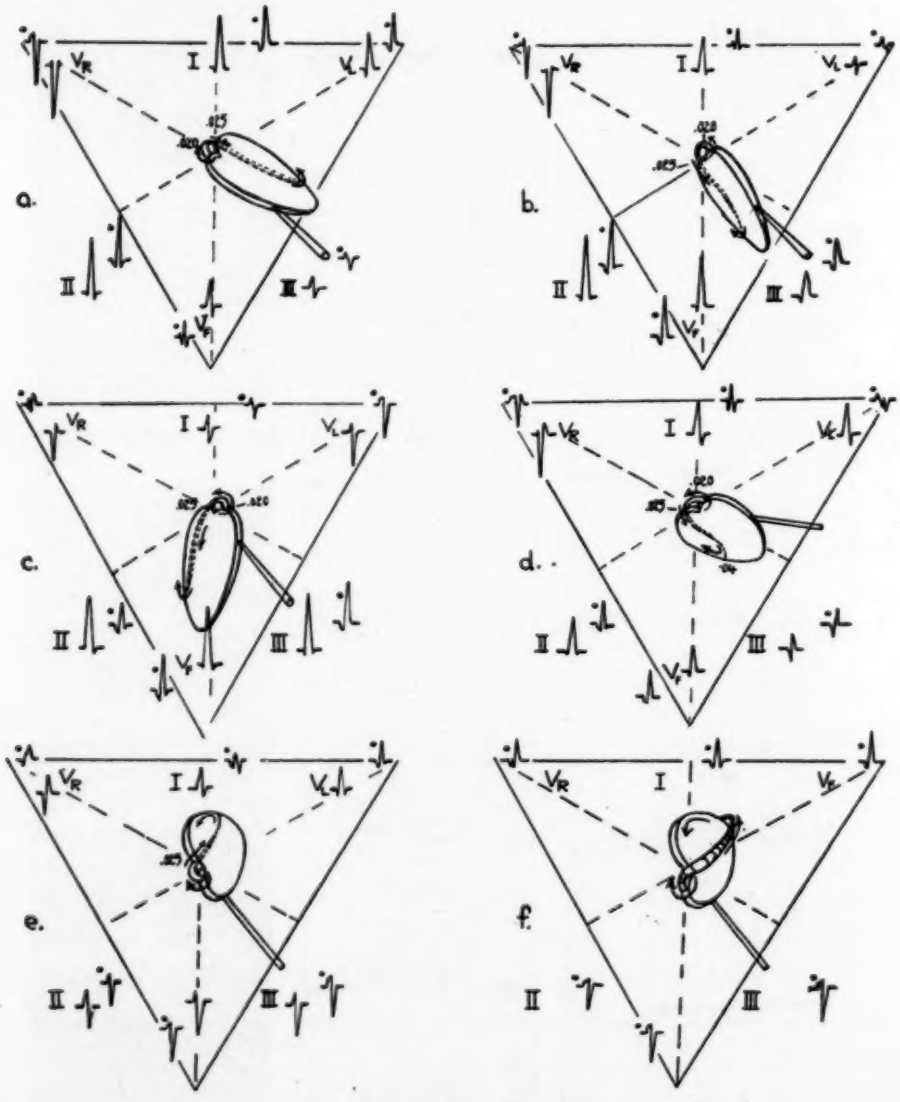


Fig. 4.—The positions and rotations are the same as those which were employed for other areas of infarction with the exception of Fig. 4,*f*. The position and rotation in the latter diagram is identical with that of Fig. 4,*e*, but an apical and diaphragmatic infarct are depicted.

For further discussion see text.

individual before one attributes importance to minor QRS variation. Also, as a result of such pathologic processes as congestive failure with ventricular dilatation, chronic pulmonary diseases, pulmonary infarction, or atelectasis, pneumothorax, abdominal distention, and many other conditions, the heart position

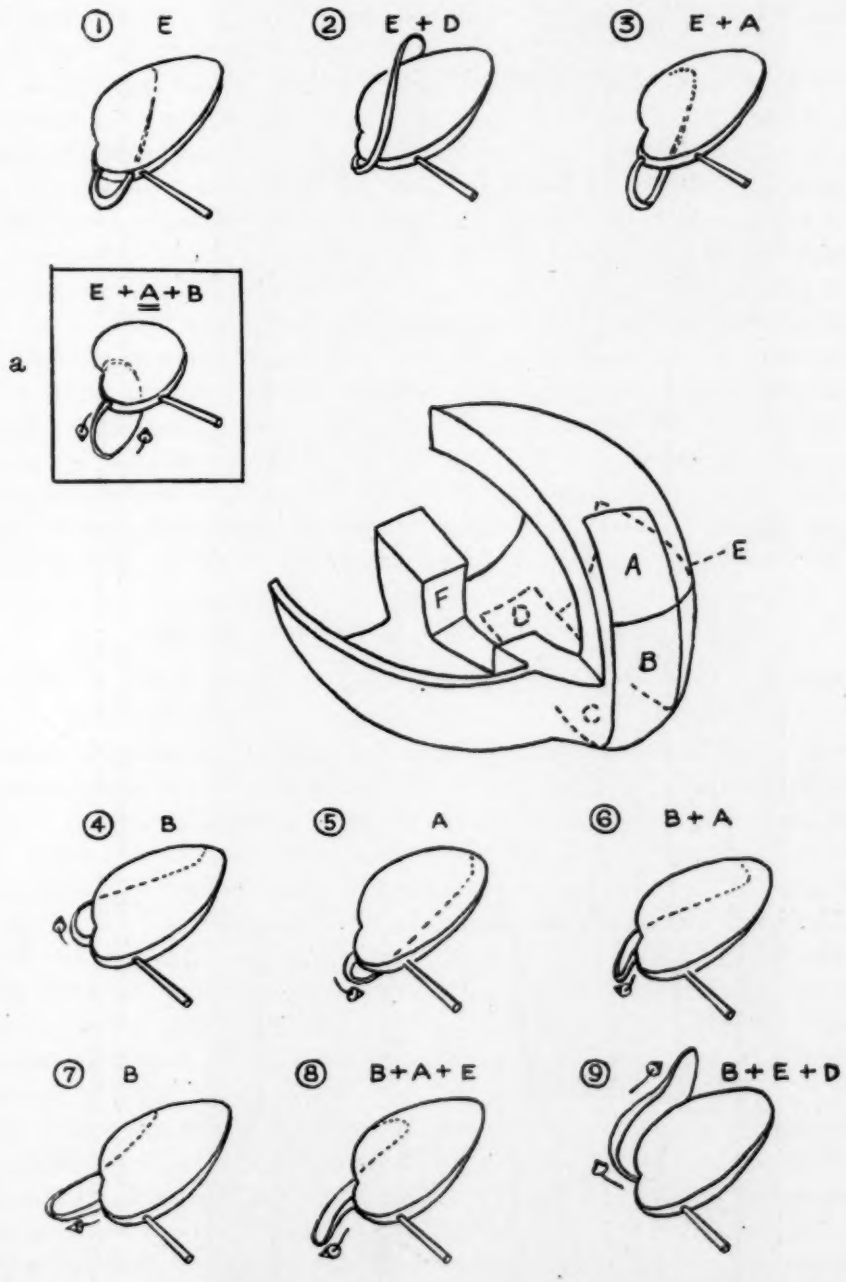
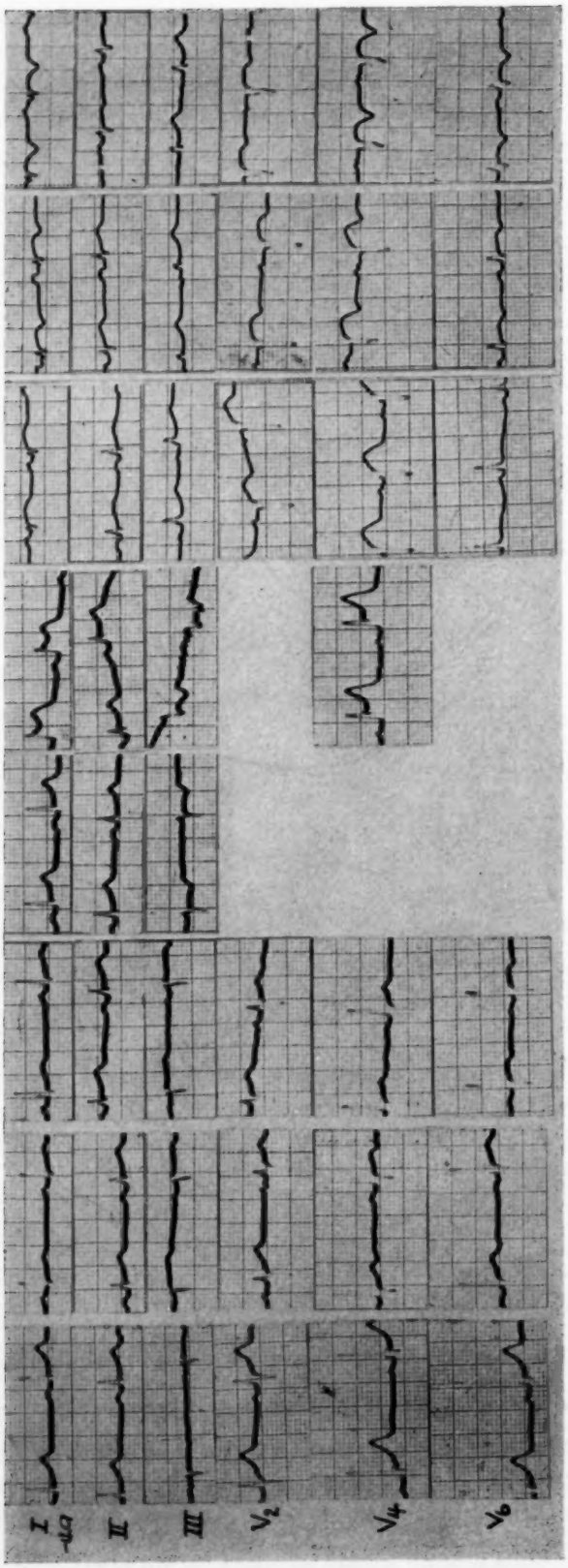


Fig. 5.—This figure shows a diagram of the ventricle in which *A*, *B*, *C*, *D*, *E*, and *F* are various common sites of infarction.

Diagrams (*1*) through (*9*), inclusive, represent the normal spatial loops and the infarct spatial loops for various combined sites of infarction.

Diagram *a* represents the normal and infarct spatial loops of a patient whose tracings before and after infarction are shown in Fig. 6.



A. B. C.

Fig. 6.—Tracings before (*A*, first three sections), during (*B*, next two sections), and after (*C*, last three sections) infarction of the anterior area A and high anterior area B extending partly into lateral area E. The loops before and after infarction correspond to diagram *a* of Fig. 5.

may be altered and thus cause QRS changes without infarction being present. In left ventricular hypertrophy and left bundle branch delay a QS complex in Leads V_1 to V_3 is frequently seen in the absence of infarction.

It should also be pointed out that the QRS changes resulting from myocardial infarction will depend to a large extent upon the size of the involved area and the location: i.e., epicardial, endocardial, intramural, or transmural.

It is our hope that none of the material presented here will be employed to erect additional empirical patterns. As much as anything else we have attempted to emphasize the fact that distinction between normal and pathologic is frequently impossible. We believe that proper evaluation of the electrocardiogram can only be achieved by some such physiologic approach as that presented here.* It is only through thinking of the QRS complex of the electrocardiogram in terms of a QRS loop which has some physiologic meaning that some sort of order can be achieved. Admittedly much remains to be understood; the hypothesis does not yet make it possible to explain everything. Furthermore, the hypothesis is not a fixed structure in our minds. It is subject to alteration to fit further observations. Some alterations have been made since 1943. Further changes in details have been under consideration for some time.

REMARKS ON ELECTROCARDIOGRAPHIC RECORDING

Failure to think of the electrocardiogram in terms of some such physiologic basis, as has been presented here, has led to the employment of various new methods of recording and analyzing the cardiac potentials. Some of these, based upon misconception at the fundamental level, have now achieved fantastic proportions. Each new method is seized upon by many without discrimination, presumably under the mistaken impression that everything which is new represents progress. While it is not a function of this paper to enumerate the errors recurring in the literature, the unipolar limb leads deserve mention, and the possibility of misapplication of the data derived from eccentricity studies and of the observations made with the cathode-ray oscillograph should be discussed in relation to the analysis of the electrocardiogram as presented in this paper.

Those who have become overly enamored of the so-called unipolar limb leads speak of these as if the electrodes are closer to certain areas of the myocardium than those of the standard limb leads, and yet they are the same electrodes employed in recording the standard limb leads. It seems to us that much error would be avoided if one thought of all the limb leads, unipolar and otherwise, in terms of the frontal plane loop as depicted here. The erroneous notion that unipolar limb leads reflected changes in the myocardium "faced" by each limb electrode better than vector analyses employing the standard limb leads, led to a regression to more empirical and more erroneous electrocardiographic interpretations than have been fashionable prior to the introduction of these notions. A deep Q or large QR ratio in V_L or V_F was regarded as a sign of infarction in the lateral wall and diaphragmatic wall of the left ventricle, respectively. This practice ignored the fundamental fact that it is impossible to determine the

*A more exhaustive presentation will appear in a future publication.[5]

magnitude or direction of a vector from only one lead, and it also ignored the simple observation that a deep Q may appear in V_L or V_F in the absence of infarction. When it is recognized that the central terminal is often not zero and that its value cannot be determined, the idea of superiority of a "unipolar" approach becomes untenable. Many pitfalls can be avoided by studying the unipolar limb leads as developed in the foregoing figures.

The cathode ray oscillograph has been employed in an attempt to record directly the spatial vector loops in the realization that if this could be done added information would be obtained. Until recently one finding incompatible with our hypothesis was represented by the fact that some of those who have recorded spatial vectorcardiograms have found that most of the loops which they encountered point forward. According to the hypothesis under discussion this would be impossible in a normal human heart which is not grossly displaced; the long axis of the loop must have at least a slightly backward direction. Until recently we have been at a loss to correlate the forward direction of the long axis of the loop with the concept of the formation of the QRS which seems to satisfy so well most of that which is observed in electrocardiograms. A theoretic inquiry into the errors of spatial vectorcardiographic technique due to eccentricity of the heart and varying eccentricity of the dipole during the inscription of the QRS furnished an adequate explanation for the lack of such correlations.[3] It is safe to say that, thus far, no method has yet been devised which records the anterior-posterior component of the loop with any degree of accuracy. The methods which have been employed have been based upon the assumption that the heart behaves electrically as if it were a dipole in the center of a sphere or a cube. Actually the heart is not even at the center of the Einthoven triangle, and the errors which are involved in the method of vector analysis of potentials measured in the limb leads are at times considerable. We have deliberately avoided application of eccentricity data in the analysis of the limb leads presented in this paper to indicate what might be achieved even if we disregarded this factor. However, the errors are much smaller than those which occur when electrodes closer to the heart (chest electrodes) are employed to measure cardiac potentials as if they were derived from a central dipole. Thus the limb leads and the frontal plane vector loop remain the most accurate electrocardiographic observations made at this time.

In our opinion the errors introduced into conventional recording by eccentricity of the heart tend to be systematic. They account, at least in part, for the exaggeration of the electrical rotation of the heart, as well as other phenomena. It has been suggested that correction for these errors be made by adjustment of the potentials of the limb leads employing the Burger triangle as a basis. Some objections must be raised to this suggestion. Even if we assume that single dipole representation is accurate and that the dipole does not move during inscription of the QRS complex, it is still obvious that the heart is not eccentric in the same direction and to the same degree in all persons. Since the shape of the triangle is dependent upon and very sensitive to the location of the dipole (Frank) the application of the same correction to all individuals is erroneous. Furthermore, in the same individual the position of the heart is dependent

upon such physiologic factors as posture, the respiratory phase, and the fullness of the stomach (among other things). Thus the acceptance of a single blanket "correction" becomes impossible even for the individual. The failure of such correction to account for the role of variation in the anterior-posterior component of the vector directions is important. Again, it seems likely that when infarction of more than moderate extent occurs the location of the representative dipole might be expected to move a sufficient distance to change the shape of the triangle in an important manner. Furthermore, the correction employing the Burger triangle (or any other triangle) involves the assumption that stationary single dipole representation is accurate for limb lead analysis in most, if not all, situations. If, indeed, stationary single dipole representation is sufficiently accurate for the normal heart it is not yet apparent that there is acceptable proof that it is sufficiently accurate for the greatly enlarged heart, for right ventricular hypertrophy, or bundle branch block. In the latter the dipole may be expected to move at least several centimeters during the inscription of the QRS complex. Actually this applies also to the normal, but in lesser degree, so that no appreciable effect is detectable.

It seems to us that for the present it would be better to retain the usual method of recording limb potentials. Familiarity with effects of eccentricity, contour, and inhomogeneity of the conducting medium makes it possible to speculate upon certain electrocardiographic problems against that background, but no mathematical method of measuring these effects as they apply in the individual, which is satisfactory for clinical purposes, has yet been found.

Finally, it is proper to ask whether even an exact mathematical correction of the limb potentials will make any material difference in the clinical interpretation of electrocardiograms, particularly for those to whom the QRS loop is only an empirical electrical phenomenon. While it is quite premature to attempt to answer the question at this time, it is important to point out that abnormal, as as well as normal vectors are subject to these errors. As a matter of fact one cannot be certain that the errors of the conventional method do not serve to "bring out" abnormalities as often as to conceal them.

Potentials at points on the surface of the chest measured against the central terminal are not accurate because the central terminal is not zero. This error is probably too small generally to be considered important from the clinical standpoint, but its recognition may lead to an understanding of some electrocardiographic problems. It is important to understand that vector analysis, as generally employed for the limb leads, is not possible in the case of the chest potentials. It is known that because the right arm, left arm, and left leg are not equidistant from the heart, errors occur in the limb leads. The assumption of centricity of the "dipole" in the chest for the precordial leads, in the recording of which the electrodes are placed at distances from the heart which may vary tremendously, combine with the contour effects to make geometric vector analysis of these potentials highly erroneous.

While there are errors even in solid angle analysis of the chest potentials, the method is closer to the truth than any other method except, possibly, the experimental. Errors involved in a simple vectorial representation of chest

potentials have been explored by Frank.[4] As Frank has pointed out, the assumption that null points lie in a plane perpendicular to the axis of the dipole is grossly false. Contour effects and eccentricity account for this. It seems clear that the contour effects are of greater importance for the chest leads than they are for the limb leads.

It is important to point out that it has not yet been shown that single dipole representation is necessarily entirely permissible. If two waves of excitation occur simultaneously, one in the right ventricular wall and one in the left, it is possible to visualize an electrical field as shown in Fig. 7. Four zero points

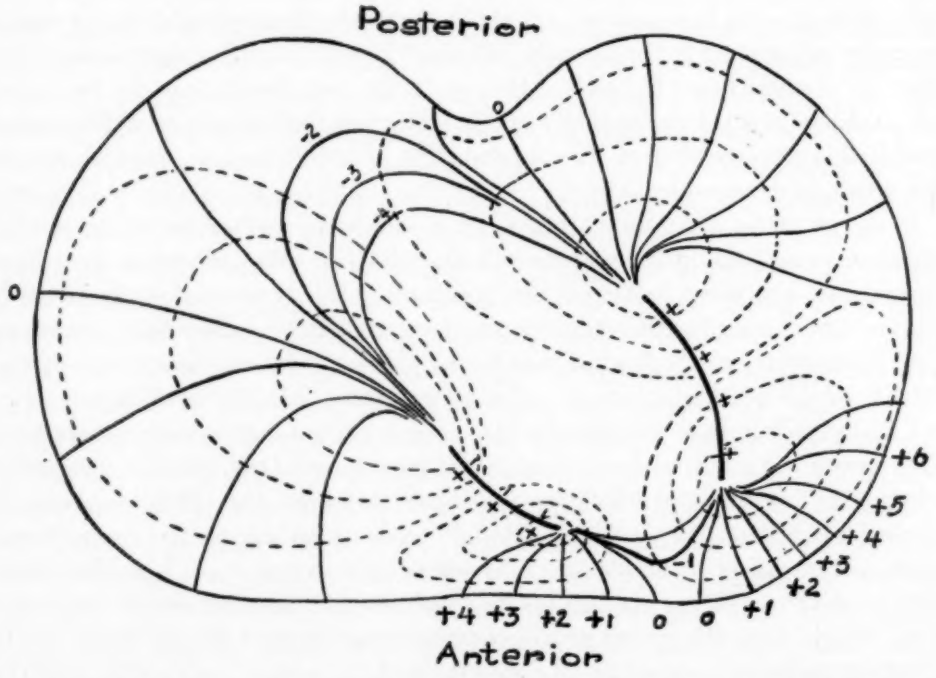


Fig. 7.—This figure shows a diagram of the electrical field which might, theoretically, be produced by two waves of excitation present simultaneously. The dotted lines are lines of current flow, the solid lines are equipotential lines. Two 0 lines are labelled at the points where they reach the surface; one in the back, the other in the right axilla. Anteriorly the zero equipotential lines reach the anterior margin at the indicated points. Thus, if the electrical field is as shown, four zero points might be found. Again, if the two waves of excitation were back slightly, the anterior zero equipotential lines might easily fail to reach the surface. They would then form a line like that shown for the −1 equipotential line. This change might take place in the same heart from time to time. It may, incidentally, be responsible for the failure to demonstrate Q waves in small anterior infarctions in some cases.

would occur and this, of course, is impossible with a single dipole. Since in the normal heart right ventricular activity is of much smaller magnitude at any given instant, and does not on the whole last long, this situation may not be easily detectable in cancellation experiments. On the other hand, in right ventricular hypertrophy and hypertrophy in both ventricles, it may be possible to detect the presence of the two waves of excitation, and it will be a bit surprising if this proves not to be the case.

With the full wave representation there is a greater tendency for the higher potentials to accumulate at the more anterior points while, with the single dipole representation, the higher potentials are more spread out laterally. The potentials in the back are affected much less.

In consideration of the present state of our knowledge of the electrical phenomena concerned in electrocardiography and the variable factors discussed above relating to limb lead and chest lead potentials (eccentricity and contour effects), we believe that the close correlation found to exist between the physiologic hypothesis of the wave of excitation as applied to myocardial infarction and the observed electrocardiograms not only lends support to the proposed hypothesis, but also makes it desirable to continue recording electrocardiograms in the conventional manner. Spatial vector techniques and knowlegde of eccentricity-contour corrections have not yet advanced sufficiently to be applicable in clinical electrocardiography.

SUMMARIO IN INTERLINGUA

Per medio del methodo del analyse del via del unda de accession, disveloppate in 1943 per Gardberg e Ashman, le autores ha analysate le alterationes electrocardiographic del complexo QRS post infarcimento myocardial in areas posterior, lateral, septal, anterior, e combinatemente ventricular. Le effectos del varie positiones electrocardiographic del corde super le resultante alterationes del complexo QRS post infarcimento myocardial es presentate graphicamente. Electrocardiogrammas illustrative es includite. Omne le patientes del presente serie esseva electrocardiographate ante le infarcimento myocardial. Assi un comparation de electiocardiogrammas pre- e post-infarcimental es possibile.

Le remanente parte del reporto consiste de remarcas in re (1) methodos de registration electrocardiographic (includente varie systemas empleate in vectocardiographia spatial), (2) le importantia de prender in consideration le effectos de eccentricitate, (3) le potential del terminal commun, e (4) le inadequatia del uso de representation dipolic in certe situationes.

Nos conclude que al tempore presente il non existe un methodo satisfacente pro le correction de errores de eccentricitate.

We should like to acknowledge the great help received from Dr. Richard Ashman in the preparation of these papers.

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THE EFFECT OF HYPERVENTILATION AND PRO-BANTHINE ON ISOLATED RS-T SEGMENT AND T-WAVE ABNORMALITIES

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INTRODUCTION

A PREVIOUS study[1] on the "juvenile pattern" in adult Negroes indicated that they were tense, anxious individuals. It was also noted that hyperventilation reproduced, and frequently exaggerated their original electrocardiographic patterns of precordial T-wave inversion. The administration of a cholinergic blocking agent consistently normalized their tracings and abolished the effect of hyperventilation.

Because relatively little is known regarding the nature and incidence of the "juvenile pattern"—particularly in the Caucasian race—this study has been extended to include a group of such patients, as well as additional Negro patients.

Emotional stress can be accompanied by transient depression of RS-T segments and flattening of T waves.[2-19] Hyperventilation may also produce similar changes.[20-24] The mechanism through which these factors influence the electrocardiogram is not known. Furthermore, the relationship of emotional tension and hyperventilation to more marked and persistent ECG abormalities, i.e., RS-T segment coving and frank T-wave inversion, has not been adequately documented or studied.

Accordingly, the admission electrocardiograms of all patients entering the Madison Veterans Administration Hospital over a two-year period were carefully reviewed. The patients who exhibited unexplained RS-T segment and T-wave changes, which were marked in degree and persistent, were then subjected to detailed cardiovascular and psychosomatic evaluation in an attempt to correlate these ECG abnormalities with emotional stress and hyperventilation.

MATERIALS AND METHODS

From May, 1952, to May, 1954, there were 862 patients admitted to the Veterans Administration Hospital, Madison, Wisconsin, who had routine admission electrocardiograms as part of their initial examination. Fifty-one of the patients exhibited unexplained RS-T segment and T-wave changes on the original tracings. In seventeen patients, the ECG pattern returned to normal with rest and reassurance, whereas in the remaining thirty-four it did not. The latter group was subjected to detailed cardiovascular study and psychosomatic evaluation.

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All patients were men. The age range was 22 to 48 years. The average age was 33. Twenty-four were Negro and ten were Caucasian. None of the patients had a history of symptoms suggesting the presence of any cardiac disease. All were found to be normotensive, and serial roentgenograms and/or orthodiascopic examination clearly established the presence of normal cardiovascular silhouettes.

The electrocardiograms obtained were taken in recumbency, employing the conventional standard bipolar leads and unipolar augmented and precordial Leads V_1 through V_6. Additional exploratory precordial leads were used in the majority of patients.

These patients were hospitalized for treatment of pulmonary tuberculosis. Five had had previous electrocardiographic studies, and in each instance the tracings were interpreted as showing organic heart disease. "Probable subacute pericarditis" had been diagnosed in four cases and "focal myocarditis" in the fifth.

Each patient was subjected to brief hyperventilation (10 to 20 seconds of forced breathing) during electrocardiographic monitoring of precordial Leads V_2 through V_6.

Thirty patients were given the vagal blocking agent Banthine or the derivative Pro-Banthine.* Initially, Banthine was administered orally in a dosage of 100 mg. every six hours (five cases). Progress tracings were obtained at 24, 48, and 72 hours during the period of drug administration. After Pro-Banthine became available, it was given intravenously to twenty-six patients. Thirty milligrams were diluted on 10 ml. of distilled water, and this was given in increments of 5 mg. at 30-second intervals. The optimal dosage was determined by the ensuing degree of tachycardia with the end point being a maximum heart rate of 140 to 150 per minute. Continuous monitoring of the electrocardiogram was carried out during the entire period of drug administration. The patients were carefully observed for any untoward reactions. The average intravenous dosage of Pro-Banthine was 20 mg., although in one patient it was necessary to give as much as 45 mg. to obtain a tachycardia of 120 per minute. Progress electrocardiograms routinely were obtained at 30, 60, 90, and 120 minutes following the injection. During the period of maximum Pro-Banthine effect, the patients were again subjected to hyperventilation for 10 to 20 seconds.

Left-sided thoracotomy for resection of residual pulmonary tuberculosis was carried out on sixteen patients. This circumstance permitted pericardial inspection.

Follow-up electrocardiograms were obtained on each of the thirty-four patients during the remainder of their hospital stay (6 to 18 months). Likewise, in the majority, progress hyperventilation studies were also carried out.

Psychsomatic evaluation was completed on twenty-six of the patients. Fifteen were evaluated at the Ward Physician's request because of their obvious emotional maladjustment, while the remainder were seen as a part of this particular study.

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*(R) Searle (Banthine Bromide—Brand of Methantheline Bromide; Pro-Banthine Bromide—Brand of Propantheline Bromide).

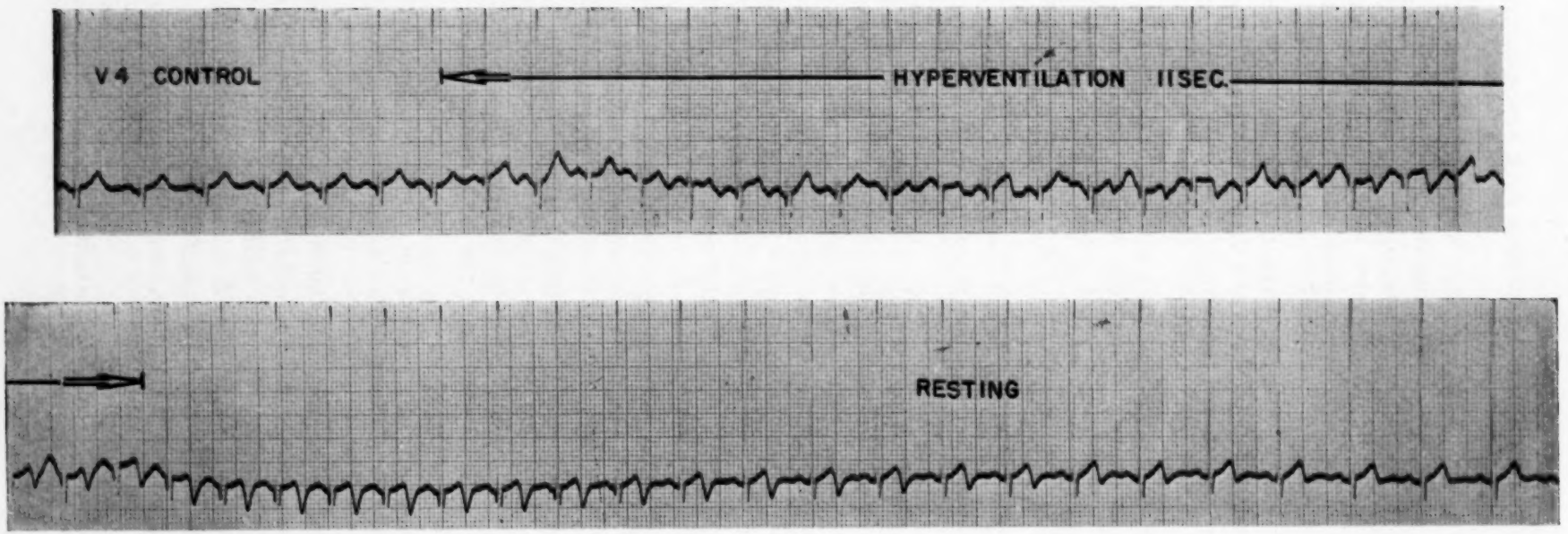

Fig. 1.—The striking RS-T segment and T-wave changes following brief hyperventilation are shown above. The T-wave inversion is shown to begin approximately 6 seconds from the onset of hyperventilation and to persist for approximately 10 seconds with gradual return to the control.

During the time this investigation was underway, a battery of psychologic tests was administered to new admissions to the hospital. These included the Wechsler-Bellevue Intelligence Scale, the Minnesota Multiphasic Personality Inventory, and the Madison Sentence Completion Form.[25] A few patients also had the Rorschach test. Accordingly, psychologic data were available on twenty-five of the patients in this series. Eight patients were not included in the testing program and one refused to be tested. There were, therefore, but two patients in the total series who did not have either psychologic testing or psychiatric appraisal. The majority of the patients had both.

RESULTS

Electrocardiographic.—

General: As noted above, there were fifty-one patients out of 862 who exhibited unexplained RS-T segment and T-wave abnormalities on their original tracings. In these electrocardiograms, the major RS-T segment and T-wave changes occurred in the right and midprecordial Leads V_1 through V_4, although in a considerable number, the left precordial Leads V_5 and V_6 showed similar alterations. For the most part, the RS-T segment changes consisted of coving, with either elevation or depression of the proximal segment. In all cases, there was frank T-wave inversion in more than one of the precordial Leads V_2 through V_6. Without exception, these electrocardiographic tracings showed normal QRS complexes, intrinsicoid deflections, and Q-T intervals. U waves were common in the precordial leads. A relative bradycardia was the rule, i.e. 60 to 75 per minute.

Patients with transient ECG changes: In seventeen of the fifty-one patients, the RS-T segment and T-wave changes reverted to normal with rest and reassurance. Brief hyperventilation consistently reproduced the original abnormalities on repeated study. In general, the electrocardiographic alterations exhibited by these patients were less striking than those in whom the changes persisted. In some of these cases, however, the RS-T segment and T-wave deviations were quite marked. For comparative purposes, representative tracings of this type are shown in Case 1.

Patients with persistent ECG changes: Among the thirty-four patients whose RS-T segment and T-wave changes persisted in spite of rest and reassurance, there were twenty-four Negroes and ten Caucasians. It is of interest that the ECG abnormalities found in the Negroes were more persistent than those of the Caucasians; often remaining "fixed" over a period of months, whereas this rarely occurred in the white patients.

In all patients, except those with the most marked changes, hyperventilation consistently exaggerated the RS-T segment and T-wave alterations. This effect was transient and disappeared soon after the hyperventilation was discontinued (Fig. 1). In the remaining instances (where the ECG deviations were most striking) hyperventilation was either without effect or produced only a minor exaggeration of the pattern.

In all of the patients who received Banthine or Pro-Banthine, normalization of the ECG pattern appeared during the period of drug administration. The

patients given oral Banthine showed this effect within 48 to 72 hours. When intravenous Pro-Banthine was used, the electrocardiographic tracing became normal in 40 to 150 minutes, with an average of 90 minutes. Ordinarily, the ECG pattern was normalized at the time that the drug-induced tachycardia had stabilized between 120 to 140 per minute.

No severe untoward reactions were noted during the administration of Banthine or Pro-Banthine; however, xerostomia and mild mydirasis were experienced by all patients. No ectopic arrhythmias were seen. Without exception, the sinus tachycardia produced by Pro-Banthine returned to normal within three hours following injection.

The majority of patients were hyperventilated during the peak of Pro-Banthine activity. In contrast to the previously noted effect of hyperventilation on the ECG, the now normalized tracing was not influenced.

The sixteen patients who had left-sided thoracotomy for definitive pulmonary resection were found to have normal pericardia on gross inspection.

Follow-up electrocardiographic study: Normal electrocardiographic tracings were obtained on follow-up study of all of the patients at some time during the remainder of their period of hospitalization (six to eighteen months). It is noteworthy, however, that hyperventilation routinely could reproduce the original ECG abnormalities of these patients.

Typical examples of initial and control tracings, the effect of hyperventilation, the normalizing influence of Pro-Banthine, as well as follow-up tracings of patients who exhibited persistent RS-T segment and T-wave alterations, are shown in Cases 2 through 7.

Psychologic.—On the basis of clinical evalution and the results of psychologic testing, it was demonstrated that the patients in this series were an emotionally disturbed group of individuals. Twenty-four were classified as having psychoneurotic reactions, six had character disorders, and two had borderline psychoses. Ten of the patients were only mildly maladjusted. The majority were quite markedly so. In general, those with more severe emotional disturbances had more persistent and more marked electrocardiographic abnormalities. Regardless of neuropsychiatric diagnostic grouping, the majority of patients studied had certain features in common. These characteristics were: (1) vasomotor instability, manifested by dilated pupils, excessive perspiration, dermographism, tremor, hyperreflexia, tachypnea, etc., (2) anxiety, and (3) overconcern with bodily function (hypochondriasis). The presence of the latter two factors was confirmed by the psychologic test results, as well as on clinical grounds.

DISCUSSION

The electrocardiographic abnormalities found in this series of patients were isolated RS-T segment and T-waves changes, i.e. RS-T segment depression and/or coving with frank T-waves inversion accompanied by normal QRS complexes. Although age alone does not necessarily preclude the existence of coronary artery disease,[26-29] this type of electrocardiographic deviation occurring transiently in a young, asymptomatic individual most often is interpreted as a

"normal variant" or explained on some "nonspecific" basis such as anemia, infection, anxiety, etc. It is in the older group, however, where the greatest difficulty arises in the interpretation of RS-T segment and T-wave changes, particulary when persistent and marked in degree. Here the tendency has been to ascribe such electrocardiographic abnormalities to "coronary insufficiency" or "myocardial ischemia."

The results of this study suggest that the benign nature of isolated RS-T segment and T-wave changes, even though marked in degree and persistent, may be revealed by hyperventilation and the administration of a cholinergic blocking agent. When brief hyperventilation exaggerates the electrocardiographic abnormalities, and when Pro-Banthine normalizes the tracing, one is afforded some objective evidence that these changes are probably "functional."

It is noteworthy that, as experience was gained from analysis of the initial electrocardiograms, certain aspects of these tracings were found to forecast their responsiveness to hyperventilation and Pro-Banthine. These are: (1) normal QRS complexes with normal intrinsicoid deflections, (2) normal Q-T intervals, (3) fairly prominent U waves, and (4) T-wave inversion occurring at the junction of the terminal T wave and the succeeding U wave.

The Negro patients in the present series can be classified from an electrocardiographic standpoint as manifesting the "juvenile pattern." All of them exhibited RS-T segment coving with frank T-wave inversion, characteristically in the right and midprecordial leads (V_1 through V_4) with lesser changes reflected in the standard and augmented limb leads. A considerable number of this group also showed similar changes in the left precordial leads. The Caucasian patients, on the other hand, showed alterations similar to the above, but these occurred less prominently in the right precordial leads. The electrocardiographic devitions in these patients were more marked in the mid- and left precordial leads. Except for the minor variation in localization of the electrocardiographic changes, there were no fundamental ECG differences between these two groups of patients.

In both the Negro and the Caucasian subjects, emotional disturbances were prominent, and the electrocardiographic pattern was significantly influenced by hyperventilation and normalized by a cholinergic blocking agent.

In a previous publication,[1] the incidence of the "juvenile pattern" in Negro men was noted to be 10.8 per cent. In the present (extended) study, the incidence was 12.5 per cent. In Caucasian men, the "juvenile pattern" (with the above noted modifications) was found in 9 out of 694 subjects (1.2 per cent).

The reason for this striking difference in incidence in the Negro and Caucasian groups is not readily apparent. It may be significant, however, that the Negro patients generally were more anxious and fearful of the electrocardiographic procedure, and were less responsive to even the most direct and forceful type of reassurance than were the Caucasian patients.

All of the patients in this study were hospitalized for tuberculosis. This circumstance is pertinent in that their prolonged hospitalization afforded an excellent opportunity for repeated electrocardiographic study over a period of many months in a relatively unchanging, though stressful environment. Emotional stress is an unfortunate accompaniment of the diagnosis and long-term

treatment of tuberculosis. The very nature of the disease involves uncertainty and anxiety on the part of the patient. Of particular importance in the present series was the apprehension associated with approaching definitive pulmonary resection. The "threat" imposed by pulmonary resection is exemplified by three of the Negro patients who had persistent electrocardiographic abnormalities preoperatively over a period of months, except for their normalization under the influence of Pro-Banthine. Postoperatively, routine tracings were normal in every instance. In numerous other cases, acutely stressful situations involving personal problems could be correlated with more marked electrocardiographic abnormalities than those which had been present on tracings prior or subsequent to the time that the acute situation existed.

Based on clinical evaluation and/or psychologic test results, thirty-two of the thirty-four patients in this series were found to have some type of neuropsychiatric or emotional disorder. Obviously, electrocardiographic abnormalities do not occur in all emotionally disturbed individuals. Why they appear in some and not in others is unknown. It is intriguing, however, to speculate about the significance of the combination of hypochondriasis and anxiety as found in the present series of patients. Conceivably, the overconcern they had relative to what was going on in their bodies, or in what way they were being manipulated (ECG study, surgical procedures, etc.), provided the qualitative or quantitative difference between these patients and the others who did not exhibit electrocardiographic changes.

Vasomotor instability was certainly not unique to the patients in this study, yet it was prominently manifested by them. This observation, plus the prompt effect of brief hyperventilation and the blocking action of Pro-Banthine, suggest that the electrocardiographic deviations found in these patients were mediated through the autonomic nervous system, most likely involving a vagal reflex mechanism. This proposal is supported by evidence that vagal stimulation can produce RS-T segment and T-wave changes in laboratory animals[30] and in human subjects.[31]

The clinical value of the observations of the present study recently has been borne out in twelve patients (mean age of 48 years) seen in consultation at the University Hospitals. Although these individuals were normotensive and had normal cardiovascular silhouettes, they were considered to be diagnostic problems from the electrocardiographic standpoint, because they exhibited persistent RS-T segment and T-wave changes. Seven of the patients had symptoms which superficially suggested coronary heart disease. Six of them had previous electrocardiographic diagnoses of "myocardial infarction" or "coronary heart disease." All of the patients were overtly anxious, tense individuals who tended to overreact to hyperventilation. Without exception, hyperventilation exaggerated or reproduced their initially observed ECG abnormalities. In five, repeated reassurance resulted in normalization of the electrocardiographic tracings. In the seven remaining patients, in whom the original pattern persisted, intravenous Pro-Banthine promptly produced normal patterns. Again, the hyperventilation effect was abolished during peak Pro-Banthine activity. On subsequent follow-up, normal tracings were obtained on all of these patients; yet, hyperventilation routinely reproduced their original ECG changes.

When one considers that these patients were emotionally disturbed individuals, it is evident that the repercussions of a diagnosis of coronary artery disease would be serious and certainly compound their psychologic difficulties. The iatrogenic aspects of this problem are readily apparent.

It is appreciated that the diagnostic value of the procedures emphasized in the present study cannot be fully ascertained until more extensive observations have been made on the effects of hyperventilation and vagal blocking agents in patients with known cardiovascular disease. To date, however, in a selected group of patients with coronary heart disease and others with well-established pericarditis (thoracotomy) the results appear to be specific for "functional" RS-T segment and T-wave changes.

SUMMARY

1. Thirty-four patients (twenty-four Negroes and ten Caucasians) with persistent and unexplained RS-T segment and T-wave changes were seen at the Madison Veterans Administration Hospital between May, 1952, and May, 1954. In none of the patients was there clinical evidence of heart disease.

2. The major electrocardiographic changes consisted of RS-T segment coving and frank T-wave inversion in the mid- and left precordial leads.

3. The administration of a vagal blocking agent (Pro-Banthine) resulted in prompt normalization of these electrocardiographic abnormalities.

4. Hyperventilation performed for ten to twenty seconds consistently reproduced the original RS-T segment and T-wave changes. This hyperventilation effect was "blocked," however, during the period of peak Pro-Banthine activity.

5. On the basis of psychosomatic evaluation and the results of psychologic testing, it was demonstrated that these patients had some form of psychiatric or emotional disorder. Regardless of the diagnostic category, however, the combination of vasomotor instability, anxiety, and hypochondriasis was prominently manifested by this group of subjects.

6. The nature and incidence of the "juvenile pattern" is discussed, as is the mechanism and role of emotional stress in ECG abnormalities of this type.

SUMMARIO IN INTERLINGUA

1. Intermaio 1952 e maio 1954 le admissiones al Hospital Madison del Administration de Ancian Combattentes includeva 34 casos (24 negre e 10 caucasian) de persistente e inexplicate alterationes del segmento RS-T e del unda T. Nulle de iste patientes monstrava signos de morbo cardiac.

2. Le major alterationes electrocardiographic consisteva de concavisation del segmento RS-T e franc inversion del unda T in derivationes precordial central e sinistre.

3. Le administration de un agente de blocage vagal (Pro-Banthina) resultava in le prompte normalisation de iste anormalitates electrocardiographic.

4. Hyperventilation de durantias de dece a vinti secundas reproduceva uniformemente le alterationes original del segmento RS-T e del unda T. Tamen, iste effecto del hyperventilation esseva "blocate" durante le periodo del activitate maximal de Pro-Banthina.

5. Super le base de evalutationes psychosomatic e del resultatos de tests psychologic, il esseva domonstrate que iste patientes habeva un o altere forma de disordine psychiatric o emotional. Sin reguardo a lor categorias diagnostic, le subjectos de iste gruppo esseva characterisate per le manifestation prominente de un combination de instabilitate vasomotor, anxietate, e hypochondriasis.

6. Le natura e le frequentia de iste "configuration juvenil" es discutite insimul con le mechanismo e le rolo de stress emotional in anormalitates electrocardiographic de iste typo.

We are grateful for the helpful advice and critical comments given by Drs. F. C. Larson, J. K. Curtis, and O. O. Meyer in the preparation of this manuscript. The technical assistance of Mrs. J. Lloyd and the secretarial aid of Mrs. F. Lee are also deeply appreciated.

The electrocardiographic reproductions were done by F. Fischer, Department of Medical Illustrations, Veterans Administration Hospital, Madison, Wis.

We are also indebted to G. D. Searle & Company for financial assistance in the cost of reproductions.

APPENDIX

CASE I.—F. Y., a 26-year-old Negro, was hospitalized in February of 1954 with residual pleural effusion on the right, and an isolated nodular focus in the left mid-lung field. His admission electrocardiogram showed T-wave inversion in Leads II, III, aV_F, V_4, V_5, and V_6, with upward convexity of the respective RS-T segments. A progress tracing taken on Feb. 25, 1954,

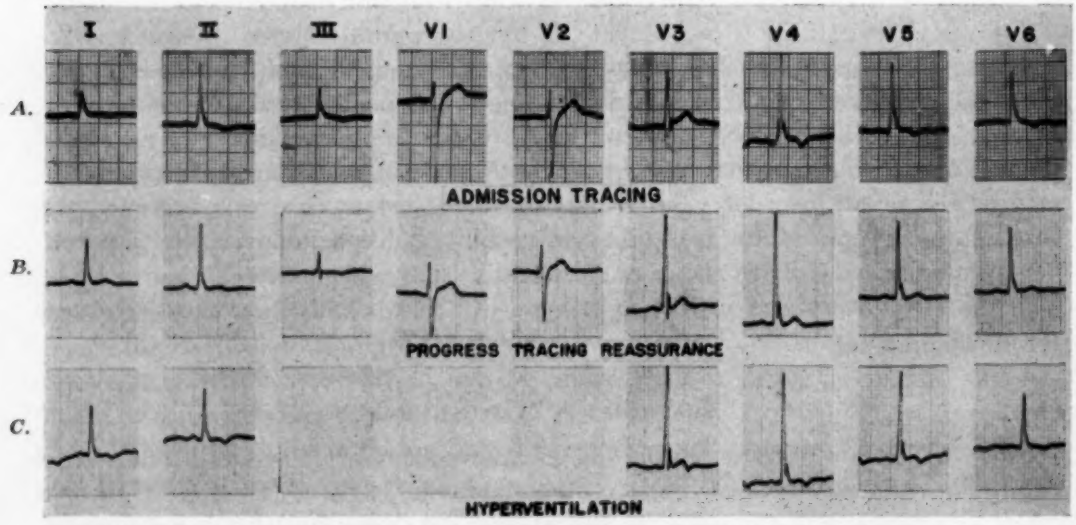

Fig. 2.—*A*, Feb. 19, 1954; *B* and *C*, Feb. 25, 1954.

after adequate reassurance, was entirely within normal limits, although an elevated take-off of the RS-T segments persisted. The effect of hyperventilation is clearly shown in the tracing of Feb. 25, 1954, with prompt and marked T-wave inversion occurring in Leads I, II, and V_3 through V_6. This tracing is entirely comparable to the admission tracing of Feb. 19, 1954 (Fig. 2).

During left-sided thoracotomy for resection of an isolated tuberculous focus situated in the lateral basilar segment, the pericardium was observed to be smooth and glistening.

On psychosomatic consultation, the diagnosis was anxiety reaction, chronic, moderate, with emotional immaturity.

CASE 2.—W. W., a 21-year-old Negro, entered the hospital with the established diagnosis of left-sided pleural effusion. Recognition of the minimal effusion was noted six months prior to present hospitalization, and appeared to be loculated in the posterolateral aspect of the left base. All studies for acid-fast bacilli were negative. There was no evidence of parenchymal pulmonary tuberculosis.

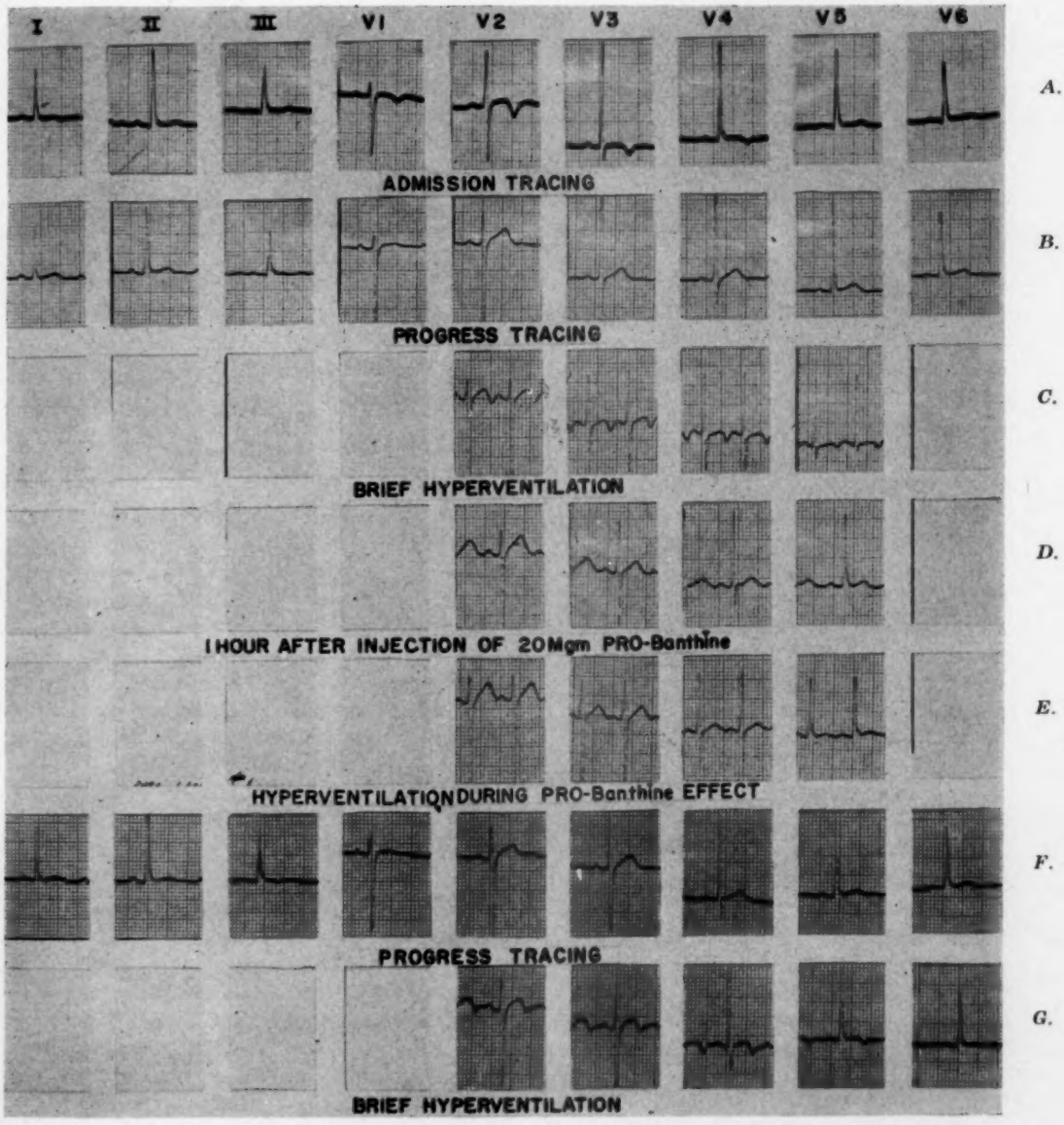

Fig. 3.—*A*, Oct. 4, 1954; *B* to *E*, Feb. 8, 1955; *F* and *G*, May 5, 1955.

His admission electrocardiogram of Oct. 4, 1954, showed marked T-wave inversion in Leads V_1 through V_4. A progress tracing on Feb. 8, 1955, after he had begun on rehabilitation, was within normal limits. Brief hyperventilation at this time resulted in prompt T-wave inversion across the midprecordial leads, simulating his original tracing. Following the intravenous injection of 20 mg. of Pro-Banthine, hyperventilation no longer resulted in T-wave alteration.

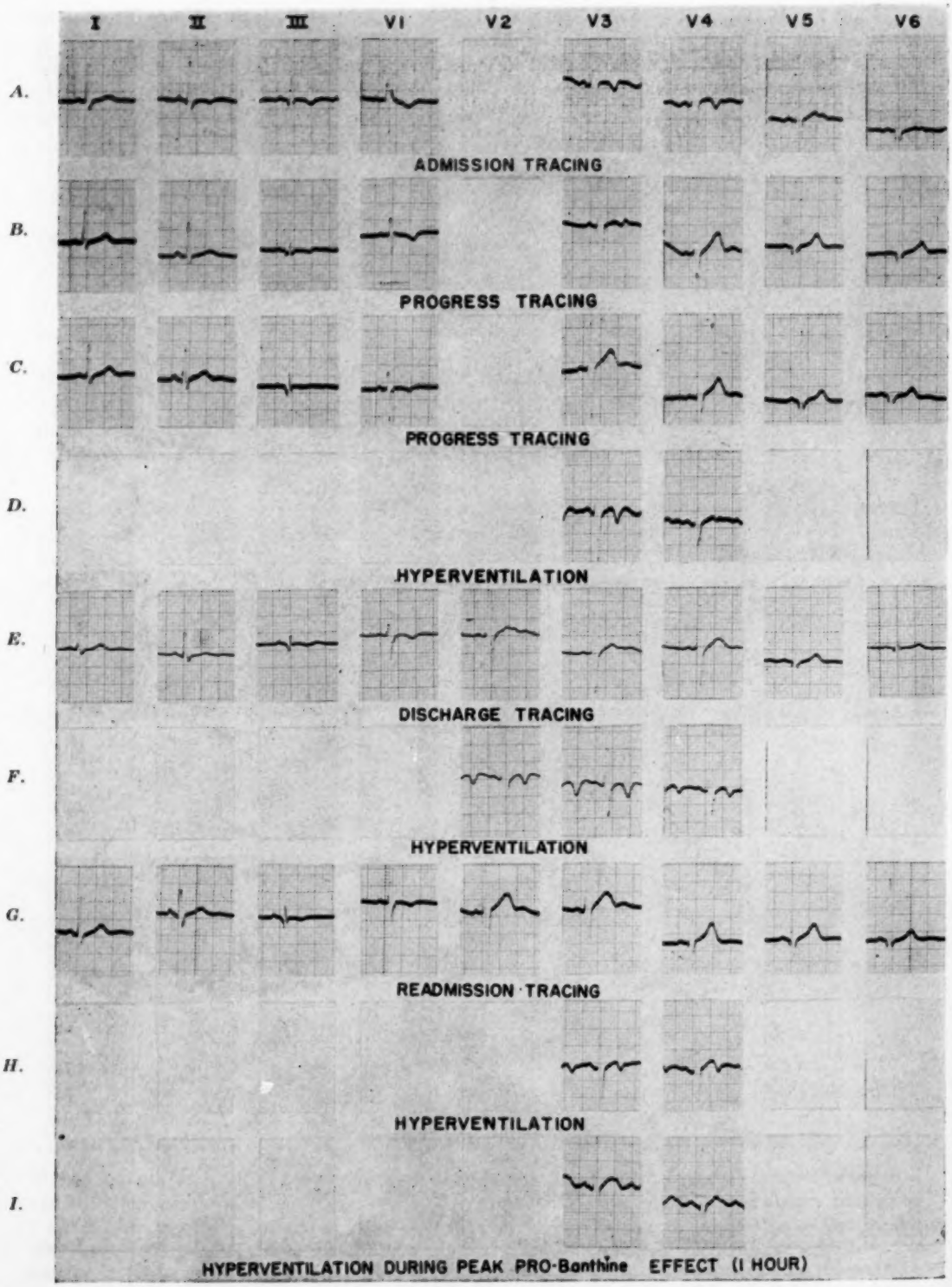

Fig. 4.—*A*, Jan. 28, 1955; *B*, Feb. 2, 1955; *C* and *D*, Feb. 18, 1955; *E* and *F*, April 20, 1955; *G* to *I*, June 10, 1955.

His most recent tracing of May 5, 1955, once again was within normal limits with marked precordial T-wave inversion occurring following brief hyperventilation (Fig. 3).

From the psychosomatic and psychologic standpoint, this patient was found to be a tense, anxious, pseudointellectual Negro. He possessed aspirations and ambitions well beyond his intellectual capacity. He readily admitted being anxious during the initial routine electrocardiogram.

CASE 3.—C. M. This 19-year-old white man entered the University Hospitals with acute rheumatic fever. He showed evidence of a soft aortic diastolic murmur, considered diagnostic of early aortic insufficiency.

His admission electrocardiogram of Jan. 28, 1955, revealed rather marked RS-T segment and T-wave changes in Leads V_3 through V_6. At this point, the question of a pericarditis was entertained. The progress tracing on Feb. 2, 1955, showed lesser changes with prominent precordial U waves. The two most recent tracings of Feb. 18, and April 20, 1955, were within normal limits. However, brief hyperventilation resulted in marked T-wave inversion in Leads V_2, V_3, and V_4, simulating the original changes which were erroneously interpreted as being due to pericarditis.

This patient made an uneventful recovery from the acute rheumatic state. He professed to have had considerable fear and uncertainty of the first two electrocardiographic tracings.

During the patient's most recent rehospitalization for tonsillectomy, the progress tracing of June 10, 1955, was once again well within normal limits. Brief hyperventilation, however, resulted in prompt inversion of the precordial T waves in Leads V_3 and V_4. One hour following the intravenous administration of 10 mg. of Pro-Banthine, previously noted T-wave inversion following hyperventilation was completely blocked (Fig. 4).

CASE 4.—T. T. This 34-year-old white man was initially admitted to the Madison Veterans Administration Hospital in June, 1953, with evidence of moderately advanced bilateral pulmonary tuberculosis. The disease was chiefly confined to the right upper lobe where there was a small cavity. His initial electrocardiogram of June 30, 1953, disclosed minimal terminal "tucking" of T_{-2}, T_{-3}, and T_{-V4}, with flattening of T_1, T_{-V5}, and T_{-V6}. The progress tracing on July 20, 1953, showed accentuation of the T-wave inversion pattern, best seen in Leads II, III, V_3, V_4, and V_5. Following the administration of Pro-Banthine, the T-wave configuration was within normal limits in all leads. A progress tracing of Aug. 21, 1953, once again showed the inverted T-wave pattern; however, the tracing of Oct. 23, 1953, was within normal limits. Hyperventilation at this time resulted in prompt T-wave inversion in Leads V_3 and V_4. The tracing taken shortly before the patient left the hospital, against medical advice, on Nov. 6, 1953, was quite similar to the tracing of July 20, 1953. The readmission tracing of Jan. 29, 1954, was entirely comparable to the tracing taken during Pro-Banthine effect and to the tracing of Oct. 23, 1953. The patient left the hospital against medical advice once again in February, 1954 (Fig. 5).

This patient was seen in consultation shortly after admission, because of long-standing and quite marked anxiety symptoms dating from the time he was grounded after a year of duty as a combat pilot. His symptoms then included excessive sweating, palpitation, insomnia, weight loss, and difficulty of concentration. The diagnosis at that time was "anxiety neurosis." He was returned to the United States for six months' rest. Subsequently, however, these symptoms continued and his return to civilian life was highlighted by considerable social and emotional maladjustment. The patient was noted to be excessively tense, anxious, repressed, and defensive. He was quite hypochondriacal and vasomotor instability was still prominent.

The I.Q. test score was 124. The MMPI and Madison Sentence Completion Form revealed the patient to be an intelligent, immature, impulsive, and rather rebellious person who was quite suspicious and resentful. He was negativistic, overly concerned with bodily dysfunction, and had rather strong psychopathic trends.

Diagnosis: Anxiety reaction, chronic, marked, in an aggressive, dependent, emotionally immature individual.

Of added interest is the fact that several electrocardiograms taken on this patient while he was in Military Service were interpreted as "active myocarditis." These tracings, however, are not available for reproductions.

CASE 5.—W. L. This 49-year-old white man was seen in consultation at the University Hospitals for evaluation of his cardiovascular status. He related the history that three months prior to his present hospital admission he had noted the onset of occasional precordial "soreness," occipital headaches, numbness and tingling in his arms and fingers, and extreme nervousness.

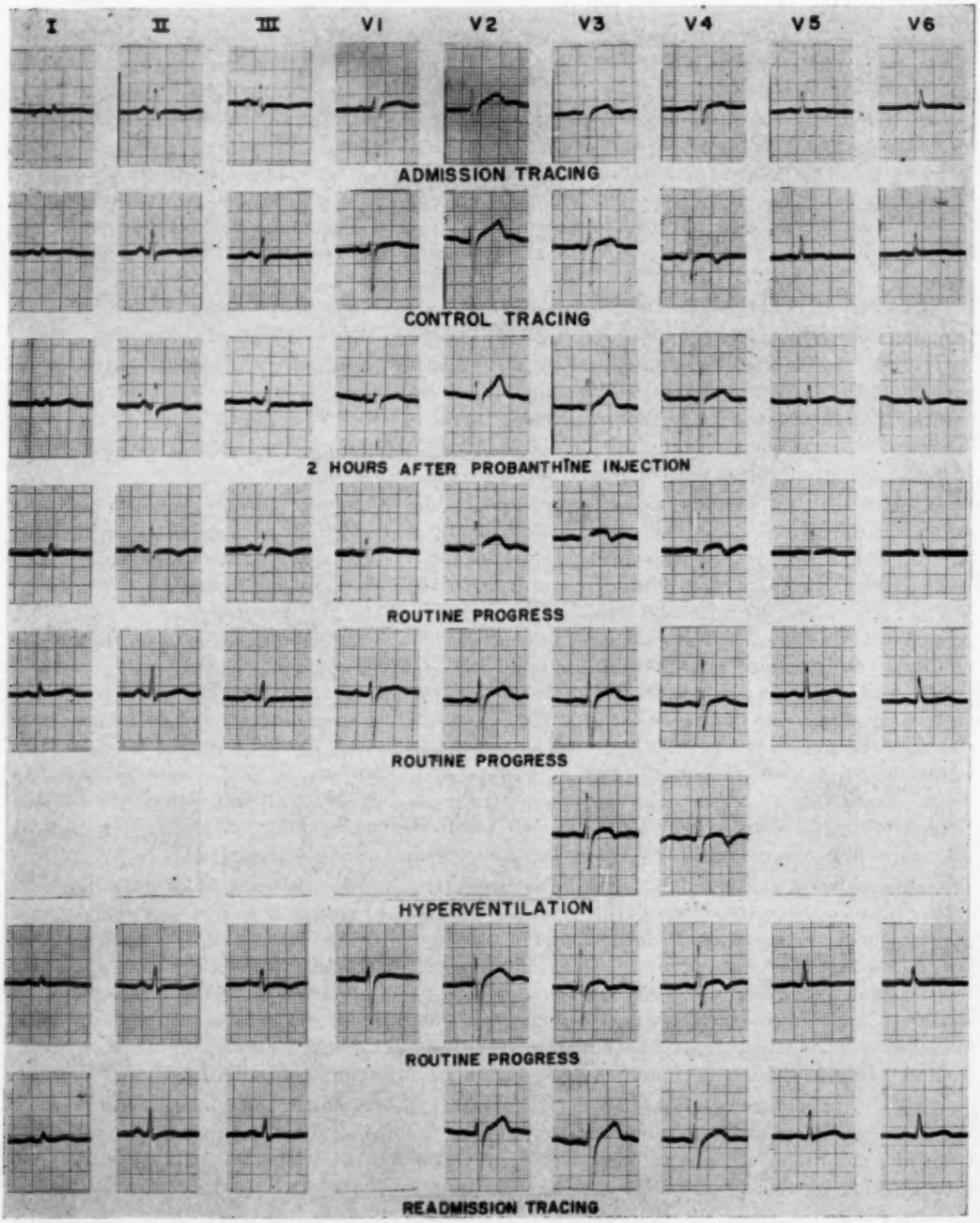

Fig. 5.—*A*, June 30, 1953; *B* and *C*, July 20, 1953; *D*, Aug. 21, 1953; *E* and *F*, Oct. 23, 1953; *G*, Nov. 6, 1953; *H*, Jan. 29, 1954.

An electrocardiogram taken prior to hospital admission Dec. 21, 1953, had been interpreted as showing evidence of "recent coronary insufficiency." This was particularly difficult for the patient to accept inasmuch as only a few months prior to this time, a close friend had died sud-

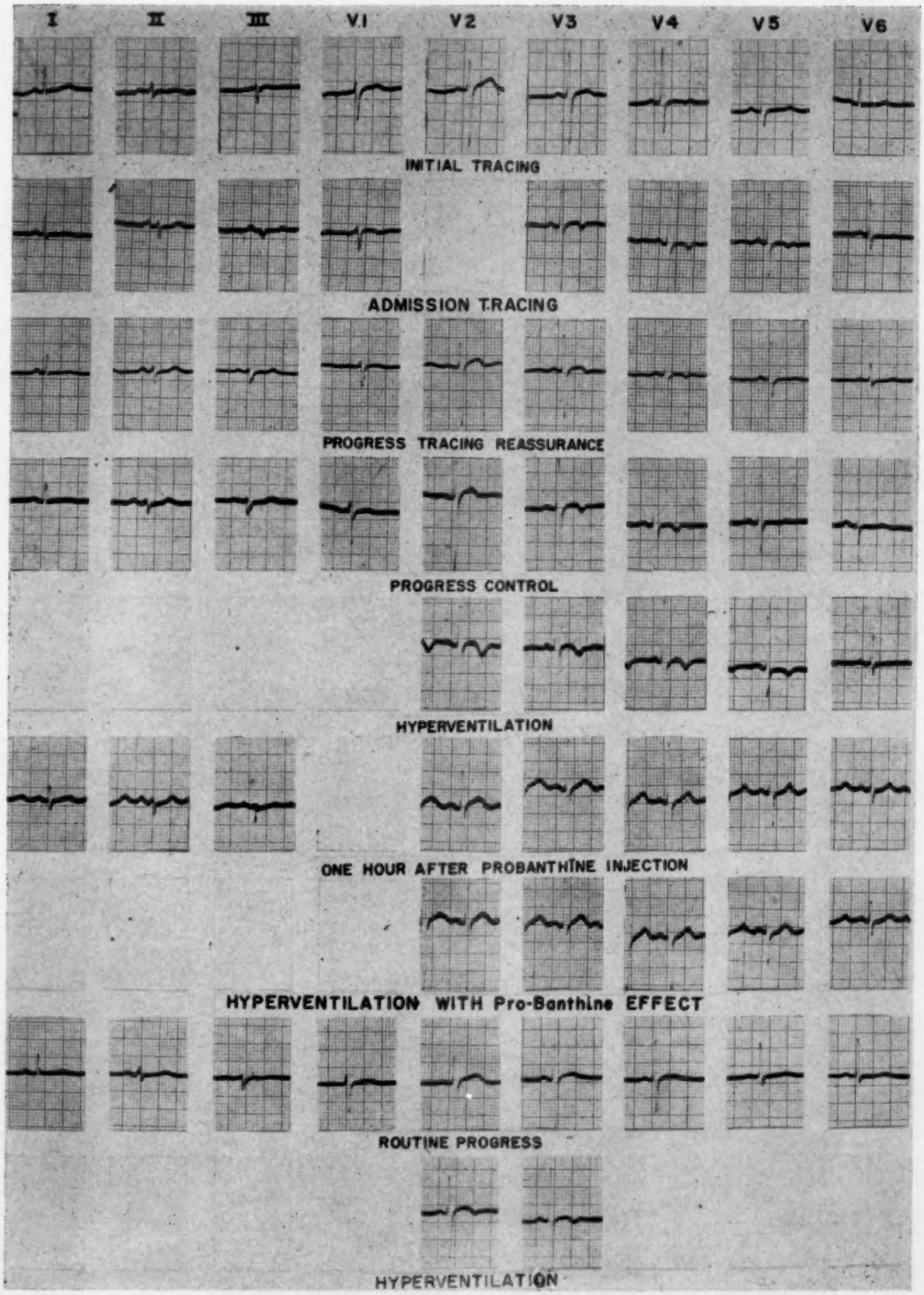

Fig. 6.—*A*, Dec. 21, 1953; *B* and *C*, Mar. 2, 1954; *D* to *G*, Mar. 4, 1954; *H* and *I*, Mar. 29, 1954.

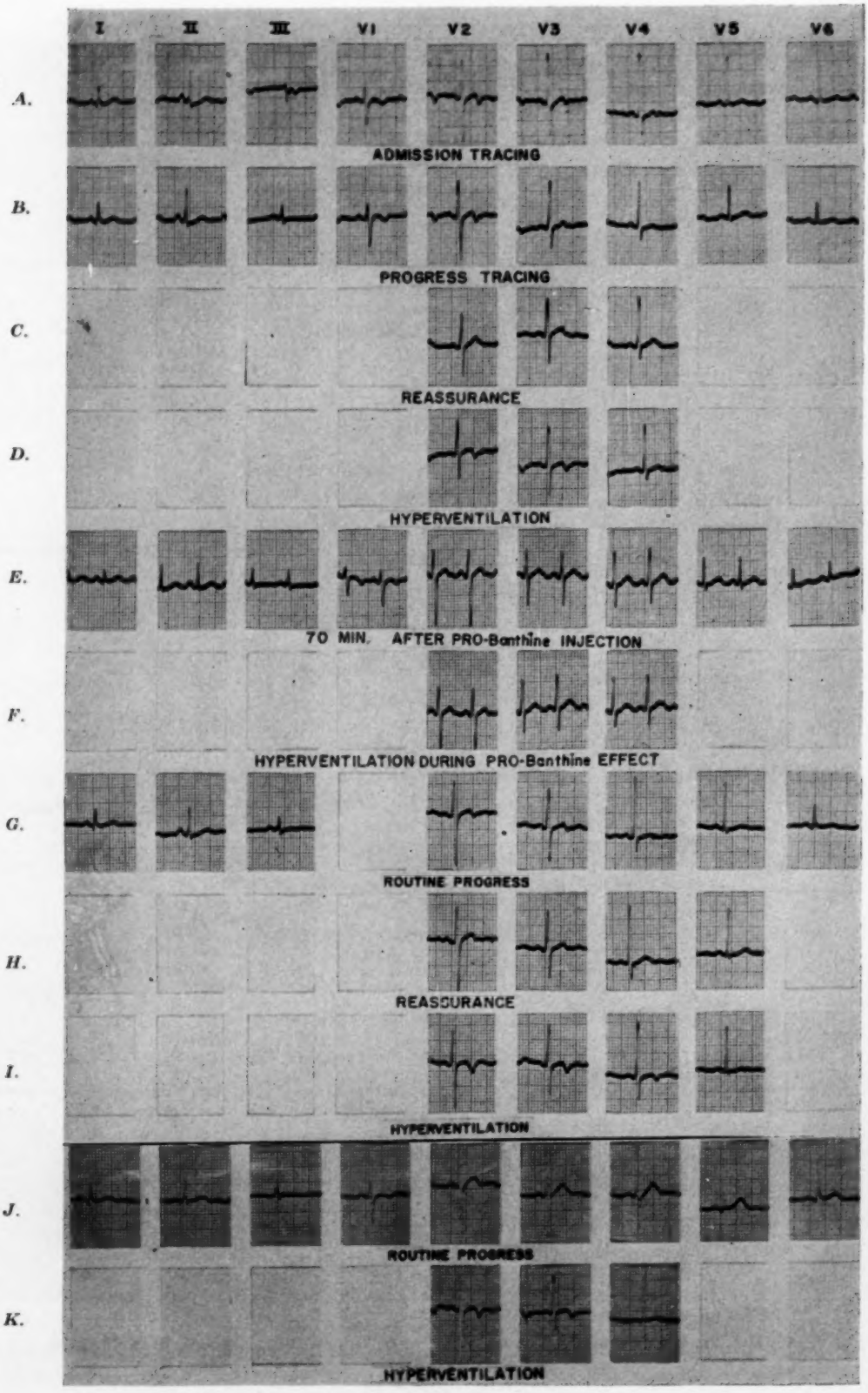

Fig. 7.—*A*, Aug. 10, 1954; *B* to *F*, Aug. 24, 1954; *G* to *I*, Sept. 14, 1954; *J* and *K*, Mar. 23, 1955.

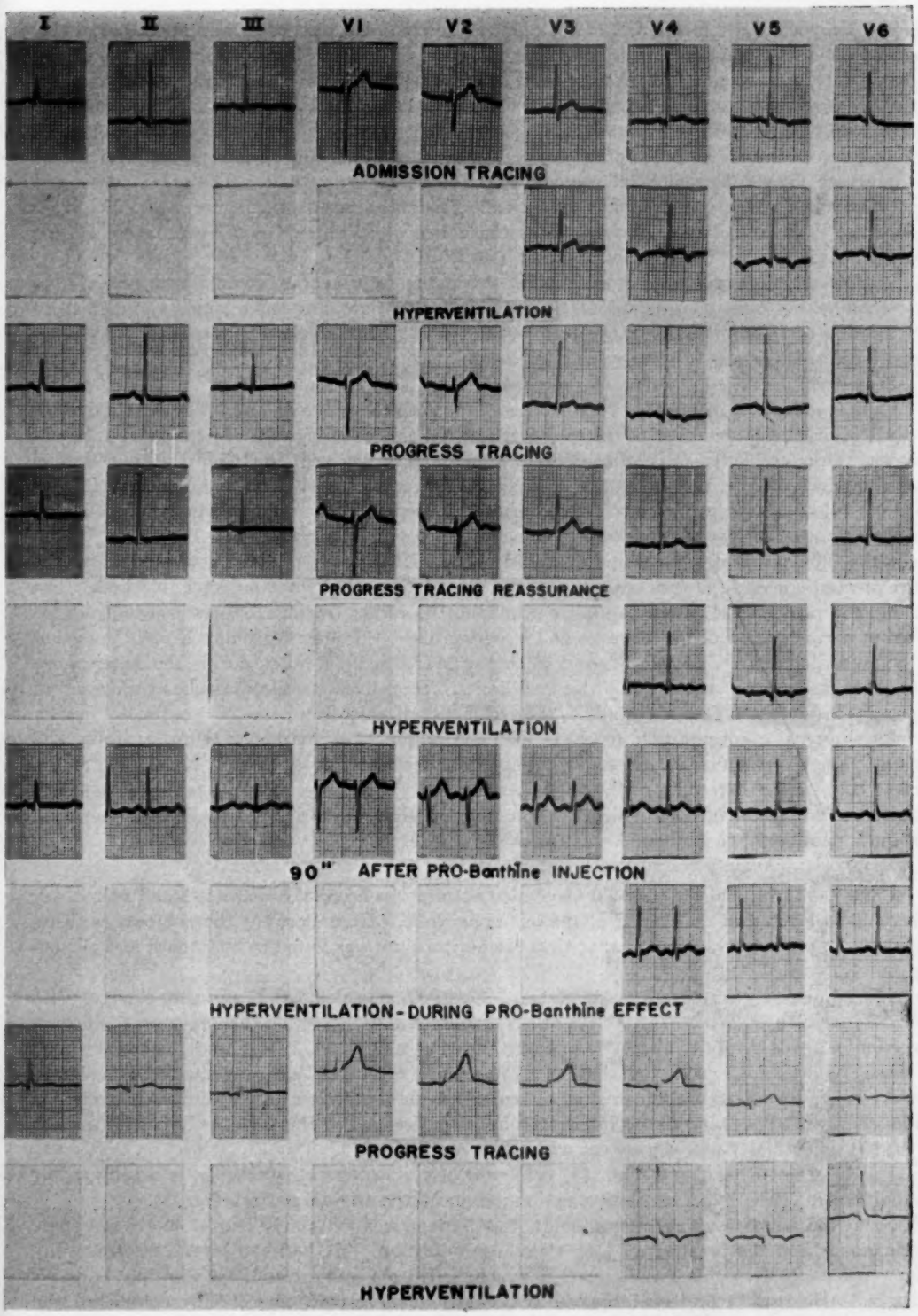

Fig. 8.—*A* and *B*, Sept. 17, 1954; *C*, Sept. 21, 1954; *D* to *G*, Oct. 6, 1954; *H* and *I*, Feb. 15, 1955.

denly of a myocardial infarction. This patient's admission electrocardiogram on Mar. 2, 1954, disclosed definite T-wave inversion across the mid- and left precordium. A progress tracing on the same date, after reassurance, showed some improvement in T-wave configuration, particularly in the left precordial leads. The progress tracing on Mar. 4, 1954, was similar to that made at time of hospital admission. Hyperventilation at this time resulted in prompt and marked T-wave inversion across the entire precordium. The tracing taken one hour following the injection of Pro-Banthine showed normal RS-T segment and T-wave configurations. The previously noted hyperventilation effect was completely blocked. His most recent tracing of Mar. 29, 1954, showed the T waves to be low upright across the entire precordium. Hyperventilation at this time resulted in prompt inversion of T_{-V_2} and T_{-V_3} (Fig. 6).

Psychosomatic consultation revealed that this patient's presenting complaint appeared at a time when he was under considerable stress in his work situation. He had a long-standing history of symptoms of an emotionally conditioned type. He was excessively anxious, tense, and hypochondriacal. There was marked vasomotor instability.

Diagnosis: Anxiety reaction, chronic, marked, with mixed somatization.

CASE 6.—T. K., a 26-year-old Negro, entered the hospital with a diagnosis of Boeck's sarcoid. Because of his clinical response to treatment, it was felt that the diagnosis of pulmonary tuberculosis was the more likely. His admission electrocardiogram on Aug. 10, 1954, disclosed T-wave inversion involving V_1, V_2, V_3, and V_4. Similar changes were noted on a progress tracing of Aug. 24, 1954. Reassurance at this time resulted in normalization of the precordial T waves, but hyperventilation produced prompt T-wave inversion in V_2, V_3, and V_4. The tracing taken under the influence of Pro-Banthine disclosed normal RS-T segments and T waves across the entire precordium, and the previously noted hyperventilation effect was completely blocked. The tracing of Sept. 14, 1954, was again quite similar to the earlier tracings. Reassurance again resulted in normalization of the T waves and hyperventilation produced prompt T-wave inversion in the precordial leads. His most recent tracing of Mar. 23, 1955, taken during the latter phase of his hospitalization, was well within normal limits. Brief hyperventilation once again resulted in prompt inversion of T_{V_2}, T_{V_3}, and T_{V_4} (Fig. 7).

Psychosomatic consultation revealed that the patient was markedly tense, anxious, and fearful. There was much vasomotor instability manifested by gross tremor, facial tics, tachycardia; cool, damp extremities; excessive perspiration, etc. Psychologic testing established that the patient was of average intelligence, emotionally labile, impulsive, fearful, hypochondriacal, and quite passive-dependent.

Diagnosis: Anxiety reaction, chronic, marked.

CASE 7.—P. M. This 26-year-old Caucasian entered the hospital with an isolated pulmonary tuberculoma located in the lingula of the left upper lobe. He underwent thoracotomy with resection in December, 1954, and at that time the pericardium was found to be smooth and glistening.

His admission electrocardiogram of Sept. 17, 1954, revealed RS-T segment changes with T-wave inversion in Leads V_5 and V_6. Brief hyperventilation produced more marked T-wave inversion in Leads V_3 through V_6. The progress tracing of Sept. 21, 1954, showed changes similar to those observed during hyperventilation. The tracing of Oct. 6, 1954, was improved as regards T-wave configuration in the left precordial leads. Hyperventilation once again brought out the initial changes. Following the intravenous administration of Pro-Banthine, only partial tucking of the left precordial T waves was seen with hyperventilation.

His most recent tracing of Feb. 15, 1955, which is a postoperative tracing, is readily within normal limits. Brief hyperventilation again reproduced the original pattern (Fig. 8).

From the neuropsychiatric standpoint, this patient was extremely fearful of the proposed thoracotomy and the prospect of long-term hospitalization. He had had several electrocardiograms taken prior to this hospitalization which had been interpreted as showing "organic changes." He readily professed that he was much more relaxed once having completed the surgical phase of his treatment.

ADDENDUM

Since completion of this manuscript, fourteen additional patients have satisfied our criteria for the "Juvenile Pattern." Ten patients were Negroes and four Caucasians. Vagal blockade

resulted in normalization of the "Juvenile Pattern" in each instance and abolished the hyperventilation reflex. Two patients in this group had an admission diagnosis of "subacute pericarditis" and, at time of thoracotomy for resection of pulmonary tuberculosis, normal pericardia were found.

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ELECTRICAL ACTIVITY IN SINUS NODE AND ATRIOVENTRICULAR NODE

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THE location of the initial activation of the auricular myocardium and the study of the activation pattern of this region is only possible in the intact heart, because of the great vulnerability of that mechanism. Lewis, Oppenheimer, and Oppenheimer (1910)[1] considered observations of this mechanism in perfused or dying hearts as useless. Keith and Flack (1907)[2] studied the anatomic structure of the sinus node and of the atrioventricular node and noted their similarity. Sanabria (1936)[3] showed, in embryological study of mammal hearts, that this nodal tissue is differentiated from the primitive myocardial tissue as a conglomeration of histologic characteristic fibers with much connective tissue in between.

It is generally assumed that both nodes have a specific physiologic function in impulse formation and conduction. Wybauw (1910),[4] using bipolar leads, demonstrated in the dog a region of initial negativity on the auricular surface. With Lewis[1,5,6] and Eyster and Meek[7,8,9] he assumed that the activation of the auricular muscle starts in this region. This point of initial negativity is in the same region where Keith and Flack could locate a sinus node anatomically. Lewis was of the opinion that this point of initial negativity coincides with the thickest part of the sinus node in the heart of the dog. He discarded the results of three experiments, because, in the first activated region, electrical phenomena were registered of a complex pattern, not found in the seven other experiments, while in two of the three experiments the region of initial negativity also shifted during the experiment: Rijlant (1936),[10,11] using bipolar leads and a cathode ray oscillograph, found a number of fast deflections of low voltage, preceeding the P wave in the sinus node region. These "presinus" deflections were found in a very small region only. He supposed that the deflections were caused by the activation of a presinus region, followed respectively by the activation of the sinus node tissue and of the auricular myocardium. His results have never been confirmed by other investigators, but our results are in agreement with his findings. Sometimes a small deflection preceding the P wave was found and considered as caused by sinus activity, but the published curves are not convincing.

The use of high fidelity apparatus proved to be of great value in the study of the electrical activation of the ventricular myocardium. We used the same apparatus for the study of the auricular myocardium and of the sinus node region.

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We constantly found, in the sinus node region, multiple fast deflections of low voltage, not registered with the commonly used instruments.[12] The activation pattern of the auricular muscle also proved to be more complex than commonly accepted.

MATERIAL AND METHOD

Technique.—This study is done on twenty-five mongrel dogs. Under intravenous Pernocton anesthesia the animal is connected with a respiration pump by an endotracheal tube. The chest is opened through a medial sternotomy and the heart exposed by distension of both sides of the thoracic cage. The pericardial sack is opened longitudinally and a cradle is made by suturing the pericardial slips to the thoracic wall. The animal in the supine position is slightly turned on its left side, allowing a complete exposure of the lateral aspect of the right auricle. The body temperature is controlled by an electrical blanket. When, during great amplification, disturbing muscle tremors have to be avoided, Flaxedil is given intravenously.

Anatomic Control.—As soon as the heart is exposed, a drawing of the auricles is made. The different points to be explored are marked in this drawing. At the end of an experiment the exact location of the electrode can be marked on the heart with India ink, facilitating the microscopic examination of the heart after Formol fixation.

Recording Methods.—A previously described[13,14] two-channel cathode ray oscillograph with photographic and viewing tubes is used. The spots on the photographic tubes are registered by a camera with a velocity of the paper film at 25 cm. per second. At two hundred milliseconds interval a signal is given on both curves.

Electrodes.—Peripheral plate electrodes of German silver are inserted under the skin of the extremities. A small spherical silver electrode with a diameter of 2 mm. is sutured on the pericardial reflection of the vena cava superior surface. Either the standard Lead II or the lead between the electrode on the vena cava superior and the left hind leg is used as a reference. A fast part in the P wave of the last type of lead is conveniently used as a reference point facilitating the study of time relations. The epicardial electrodes are of a special kind. We use differential (proximal bipolar) electrodes with a distance between the lead points of 0.1 to 0.2 mm. or less. These silver lead points are isolated from each other and consist of two extremely small globe segments protruding from a pencil-like perspex holder (Fig. 1). Without applying too much pressure, a satisfactory contact of the electrode with the auricular myocardial surface is attained. A bipolar lead between two proximal lead points is called a "differential" lead. This type of electrode is called "differential epicardial electrode."[14,15]

Only the action potentials of the small region of the myocardium immediately under the differential electrode are registered (Clement and Garten[17]). Such a differential lead allows the estimation of the moment of activation and of the direction in which the activation wave is conducted. The activation wave is considered as a dipole front.[18] If this dipole front arrives at the same moment at both lead points, none or only very small potential differences become apparent.

This means that the dipole front is parallel to a connecting line through both lead points.

By carefully rotating the electrode, this connecting line through both lead points is turned in a direction perpendicular to the dipole front, which now passes the lead points in succession. The moment this dipole front arrives between these lead points, the greatest possible potential difference exists. A single sharp differential spike is registered, which shows a maximal deflection when the line through both lead points is parallel to the direction in which the activation front is conducted. The vortex of this spike gives exactly the moment of activation of the small region under the differential electrode.[13] (Fig. 2).

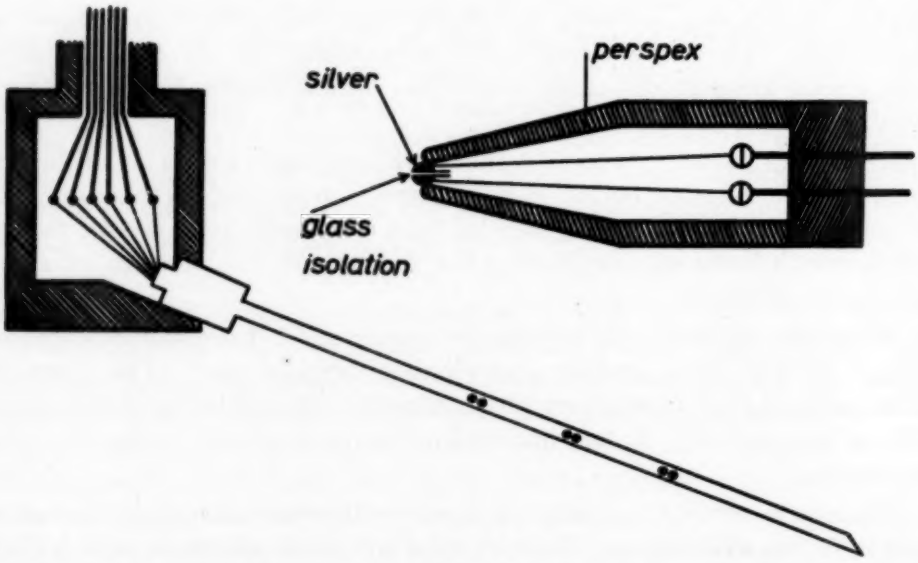

Fig. 1.—Right: Differential electrode used for leads of sinus node. The silver lead points consist of two small globe segments isolated from each other by glass. The distance between the lead points is 0.1 mm. Left: Three-differential needle electrode of special form, used for exploration of the atrioventricular node region.

Unipolar epicardial leads are taken, using one of the lead points of the differential electrode, with the left hind leg as distant electrode.[19]

A unipolar complex of the auricular surface usually shows a biphasic complex with a large fast deflection, the intrinsic deflection. In this deflection a rapid component can be distinguished. The use of a differential electrode gives the opportunity for recording simultaneously differential and unipolar leads from exactly the same area. The rapid component of the intrinsic deflection of the unipolar complex corresponds exactly with the vortex of the spike in the simultaneous differential lead. This is in agreement with our earlier experiences in the ventricular myocardium.[14,15]

After some experience is acquired, it is possible to keep this kind of electrode during a certain time on the same spot of the auricular surface. An extremely small displacement of the electrode results immediately in changes of the com-

plexes on the viewing tube and of the registered curves. If too much pressure is applied by the electrode on the myocardial surface, S-T-T deviations immediately appear.

Criteria.—Only those curves are considered in which the zero line is stable, at least two successive complexes are identical, and no S-T-T deviations exist.

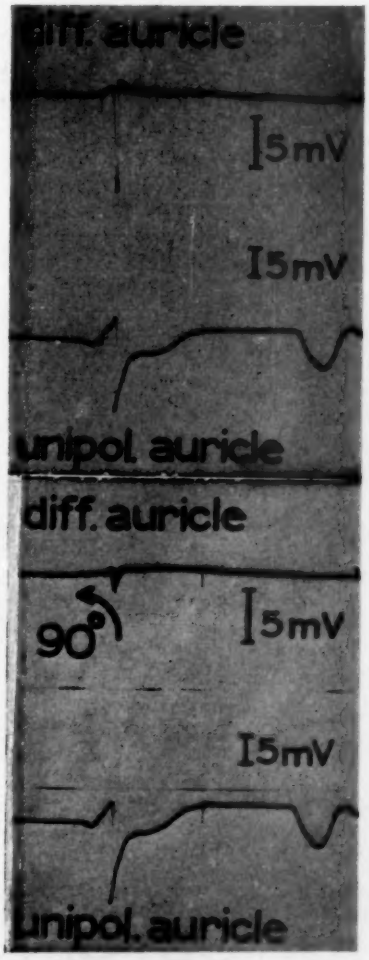

Fig. 2.—Upper tracing: In the differential lead of the auricle a sharp spike is seen, coinciding with the intrinsic deflection in the unipolar lead of the auricle. In this position of the differential electrode, the connecting line of the lead points is parallel with the direction of propagation of the activation wave. Lower tracing: The differential electrode is now turned 90 degrees. The connecting line between both lead points is now perpendicular to the direction of propagation. In this position the differential complex shows only a very small voltage.

RESULTS

Activity of the Sinus Node.—In only a very small area of the auricle is found a region in which the initial positivity is absent and the complexes are wholly negative in unipolar leads.[16] This area is located in the sinus node region.

Outside the small circumscript area of initial negativity we did find some initial positivity. In the immediate surrounding area the predominantly negative P wave is already preceded by a small positive deflection. When the distance

to the point of initial negativity increases, this positive deflection becomes larger. In some experiments we did not find an area of pure initial negativity. In these cases we assumed that the center of primary activity was located somewhat distant from the epicardial surface or that this center gave way to the slight pressure of the epicardial electrode.

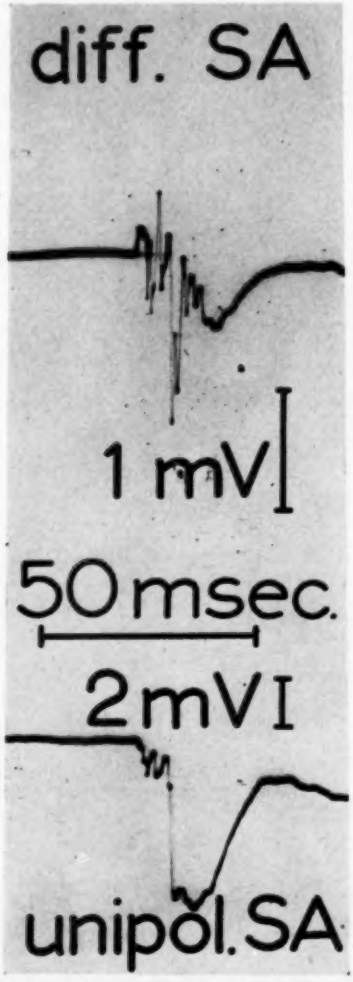

Fig. 3.—The lower tracing is a unipolar complex of the pacemaker region of the sinus node. The complex is entirely negative; mainly the descending limb shows many notches. The upper tracing is a simultaneous differential complex of the same place. Many fast spikes are seen. The tracing is slightly retouched.

The location of the initial negative area is not completely similar in different hearts and can change more or less during the experiment. Usually this initial negative area is found in the region of the taenia terminalis near the corner between the vena cava superior and the right auricular appendage. Sometimes it is located 1 cm. or more caudal to this point (in the direction of the tail of the sinus node) or just around the corner on the medial wall of the auricular appendage, where it is in connection with the vena cava superior. The unipolar complex in this area of the anatomic sinus node has an interesting pattern (Fig. 3,

lower tracing). In the descending limb of the P wave there are many notches present. The smooth form, registered with ordinary recording instruments, is absent. The differential complexes of points in this region have a very complicated form consisting of multiple spikes (15 to 25) of low voltage. This differential sinus complex is most characteristic in the area where the pure initial negativity exists (Fig. 3, upper tracing). It starts before any other sign of auricular activation, preceding the chief negative deflection of the simultaneous unipolar lead with some milliseconds and preceding the beginning of the P wave in Lead II with approximately 25 milliseconds (Fig. 4). We presume that this complicated differential complex is the result of the local activity of the pacemaker region. It is always found in a small circumscript area of the sinus node, and nowhere else. The voltage is considerably lower and the duration of the differential sinus complex (10 to 18 milliseconds) is longer than the duration of the differential complex elsewhere on the auricular myocardium (4 to 8 milliseconds).

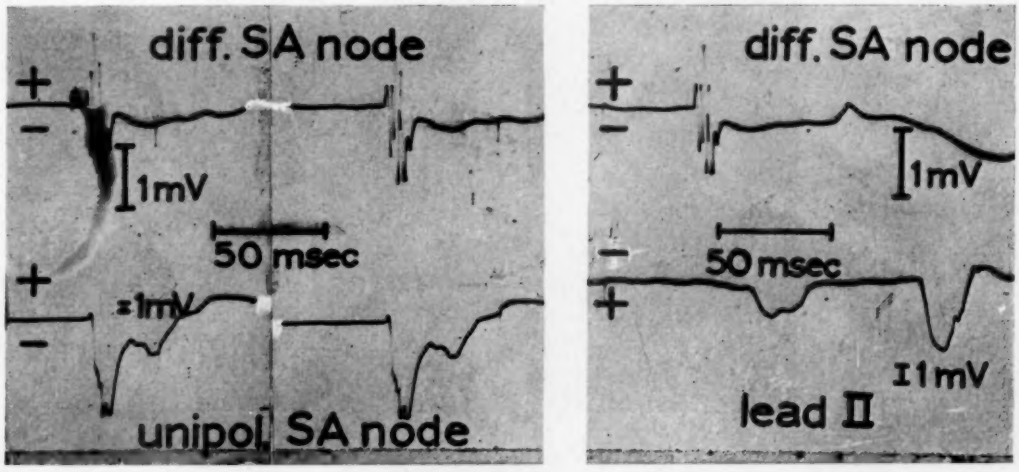

Fig. 4.—The upper tracing shows three differential sinus node complexes of the same place, taken with a time interval of about thirty seconds between the complexes. Note the similarity of the pattern of those differential complexes. The lower tracing shows, successively, the leads taken simultaneously with each of the differential complexes. The unipolar complexes of the sinus node show a small initial positivity, indicating that the records are not taken exactly from the very first activated region. The reversed Lead II demonstrates the time relation with the differential sinus node complex.

Sometimes during an experiment we get a shifting of the area of initial negativity and, simultaneously, a shifting of the differential sinus complex in the direction of the tail of the sinus node. Several reasons can be given:

1. The pressure caused by the epicardial electrode is too strong.
2. The temperature of the animal is not kept constant.
3. The myocardial surface is exsiccated.
4. The experiment is overprolonged.

The location of the sinus activity is more constant when the body temperature of the animal is regulated and if the epicardium is moistened with physiologic saline solution of the same temperature.

Under favorable conditions the multiple fast deflections of this local sinus activity are preceded by a few small, slow fluctuations (Figs. 5 and 6). It is possible that these "prepotentials" are of importance for the impulse formation in the sinus node (Arwanitaki, Bozler, Weidmann[20-24]). No delay of the activation between the sinus node region and the surrounding myocardium is seen.

In the hearts of two dogs the region of sinus activity was examined microscopically. It appeared that the electrical sinus activity is indeed localized in the area where anatomically the cranial part of the sinus node is located. Here we find an area which has, more or less, the anatomic characteristics described by Keith and Flack. They concluded: "There is a remarkable amount of primitive fibers persisting at the sino-auricular junction in all the mammalian

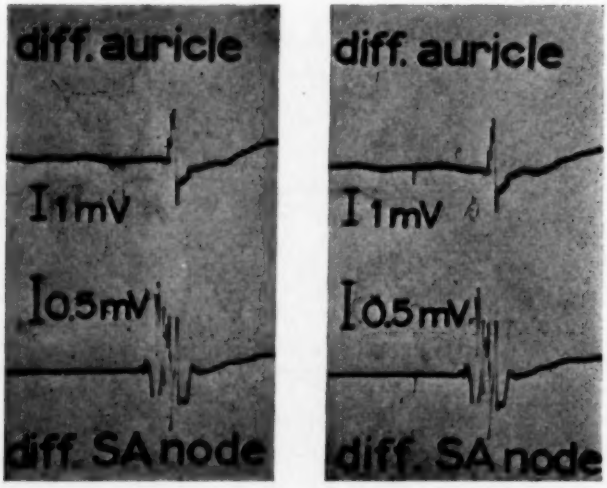

Fig. 5.—Upper tracing: Differential complex of auricular myocardium close to the sinus node. On the ascending limb some small notches are seen. Lower tracing: The typical pattern of a differential sinus node complex is seen. Note that the electrical activity in the sinus node still exists, when the auricular myocardium surrounding the node is already activated. In both leads two successive differential complexes are shown.

hearts examined. These fibers are in close connection with the vagus and sympathetic nerves and have a special arterial supply; in them the dominating rhythm of the heart is believed to normally arise." They described a central artery, surrounded by connective tissue in which many typical muscle fibers, nerves, and ganglion cells are seen in the sinoauricular junction of human hearts. The musculature of the vena cava superior and of the right atrium communicates on both sides of the central artery. The sinoauricular junction is marked by a thickening of the heart wall at this point. The amount of sinus nodal tissue varies, but in the neighborhood of the taenia terminalis some specific tissue can always be found. The above-mentioned typical muscle fibers of the sinus node are striated, fusiform with elongated nuclei, and surrounded by compact connective tissue. Macroscopically, these typical muscle fibers have a paler color than the common auricular muscle fibers.

In the heart of the dog we found the muscle fibers of the sinus node surrounded by compact layers of connective tissue, but the difference between those muscle fibers and the ordinary myocardial muscle fibers is extremely slight. A well-defined borderline between nodal tissue and the surrounding myocardium does not exist.

Electrical Stimulation.—By electrical stimulation of the auricular wall, auricular extrasystoles appear. From such a focus the activation front spreads out over the myocardium and also arrives in the sinus node region. In this case the sinus node region is not the first activated part of the auricle and behaves electrically like ordinary myocardial muscle. The complicated differential sinus complex is substituted by a differential spike of a more simple form, sometimes

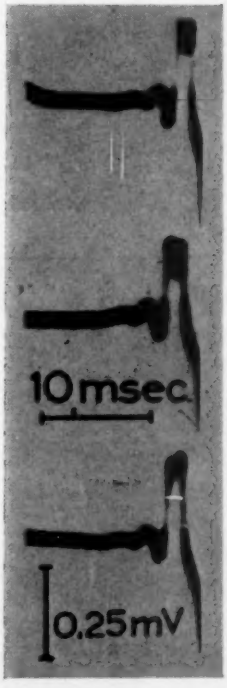

Fig. 6.—In a few experiments, two to three small slow potential fluctuations are seen preceeding the fast phenomena of sinus activity (see Fig. 5). To demonstrate the constancy of these slow fluctuations, the "prepotentials" of three successive sinus node complexes are shown.

identical with the normal auricular differential spike (Fig. 7). The sinus node can be driven by the electrical stimulation if the stimulating frequency is slightly higher than the spontaneous frequency of the node. During this type of stimulation of the sinus node region the complicated differential sinus complex is sometimes substituted by a much less complicated complex. After termination of this electrical stimulation, the original spontaneous sinus activity returns gradually.

A tracing of the differential lead of the center of sinus activity, during electrically induced fibrillation of the auricles, shows progressive disintegration of the characteristic complexes of sinus activity. Within one second or less the

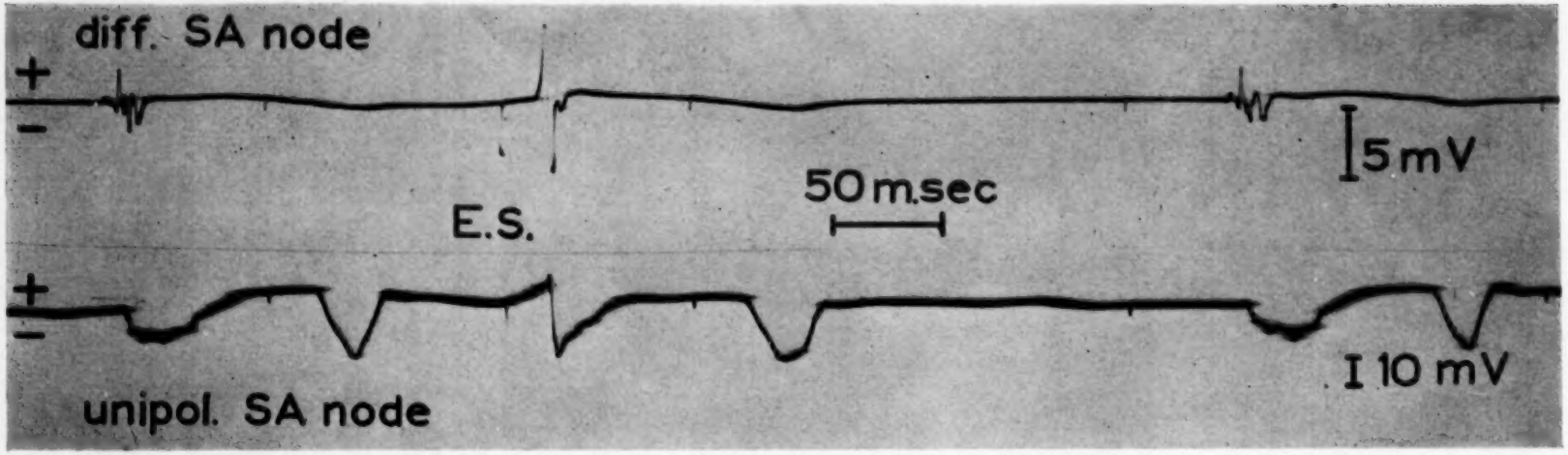

Fig. 7.—Upper tracing: Differential complex of sinus node. Lower tracing: Unipolar complex of sinus node. The second beat is an auricular extrasystole provoked by electrical stimulation of the right auricular appendage. The complicated differential sinus complex disappears during the extra systole. A spike of a simple form is seen, with a similar form as the common differential complexes elsewhere on the auricular myocardium. In the unipolar lead a biphasic complex of a smooth form is seen. The third beat is originating again in the pacemaker region like the first beat and has the typical multiphasic pattern of local sinus activity. Conclusion: During auricular extrasystoles, the sinus node region is activated as the auricular myocardium.

differential complexes of the sinus node region are identical to the complexes elsewhere on the auricular surface during fibrillation. When normal sinus rhythm is resumed, the typical differential complexes of local sinus activity gradually reappear.

ACTIVITY OF THE ATRIOVENTRICULAR NODE

Technique.—If a differential needle electrode is brought in contact with the anatomic region of the atrioventricular node by way of the sinus coronarius, a similar type of complicated complex can be found. This needle electrode is, in principle, the same as we used in the left ventricular wall experiments[13,14] (Fig. 1).

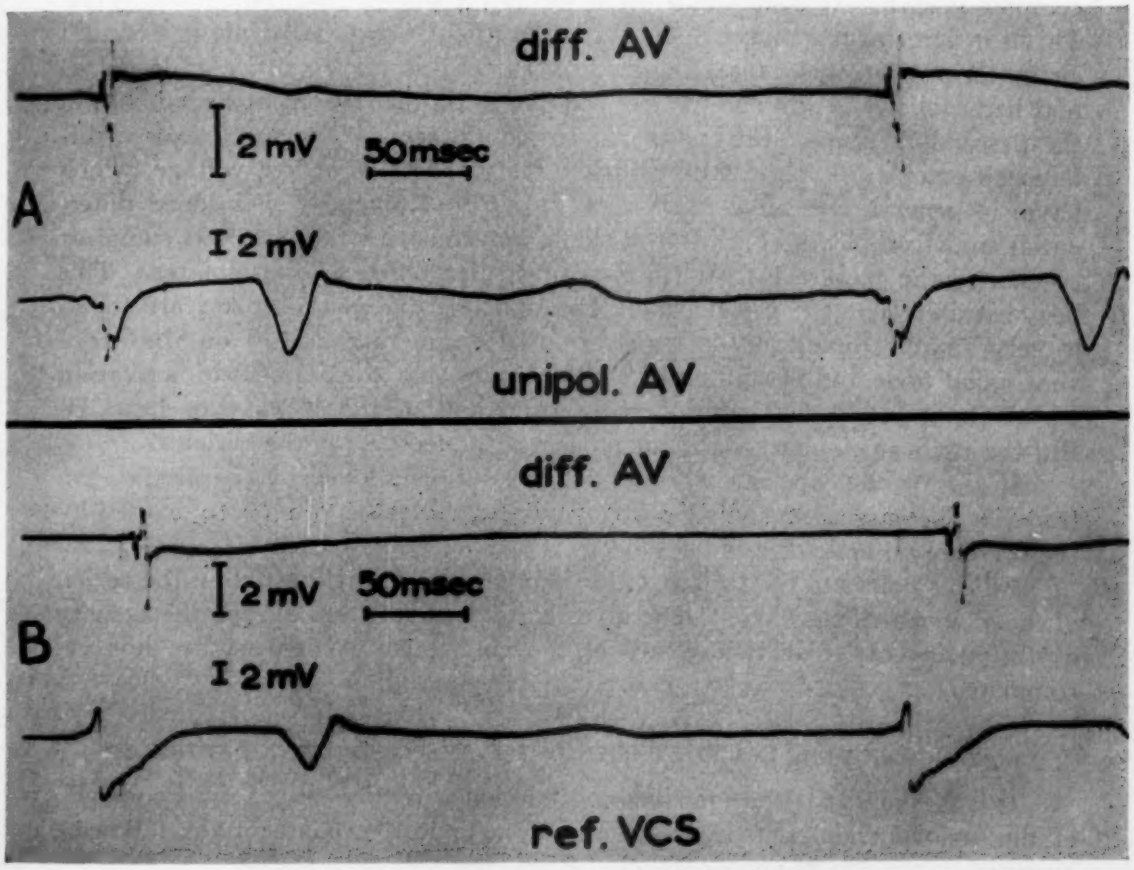

Fig. 8.—In the upper tracings of row *A* and of row *B*, differential complexes of the atrioventricular node are seen. They consist of multiple fast spikes, which coincide with the notches in the lower tracing of row *A*, the unipolar lead of the atrioventricular node. The initial positivity of those unipolar complexes of the atrioventricular node is often much more distinct. In row *B* it can be seen that the differential complex of the atrioventricular node coincides with a point late in the auricular cycle.

A needle electrode with three pairs of proximal bipolar lead points (three-differential needle electrode) is inserted in the right auricular cavity via the sinus coronarius. A finger of the free hand is placed as near as possible to the region of the septum membranaceum, between the medial right auricular wall and the

aorta ascendens. It is possible to palpate the point of the needle here through the auricular wall. In an opened heart we find that a needle, inserted in this way, is resting against the lower part of the interauricular septum. This is the area where the anatomic atrioventricular node is found. Guided by the form of the complexes on the viewing tubes of the oscillograph, the differential needle is moved and rotated carefully. In this way one of the three differential electrodes is put in position on top of the atrioventricular node. In experienced hands the needle electrode can be kept for some time in exactly the same place.

RESULTS

In unipolar leads of the interauricular septum an initial positive biphasic complex is seen. In differential leads we find a single, fast, differential spike. This is in agreement with the findings on the auricular surface. Only in a certain circumscript area is a more complicated pattern seen. In unipolar leads we find here, following the more or less positive initial deflection, many notches in the descending part of the complex. In simultaneous differential leads a differential complex is found with multiple fast deflections of low voltage, which have, in general, the same characteristics as the previously mentioned differential sinus complexes (Fig. 8). A slight movement of the needle is sufficient to change the picture into the normal auricular differential complexes. This demonstrates that the region where the multiple differential spikes are found is very small. Simultaneous registration of a differential lead on the atrioventricular node and of standard Lead II proves that the moment of activation of this small area occurs during the second half of the P wave of Lead II. But the atrioventricular node is not the last activated part of the auricles.

If, during the experiment, too much pressure is applied by the needle electrode, an incomplete or complete atrioventricular block is often seen, caused by the pressure on node or bundle.[25]

All this points to the fact that the differential needle is located in the region of the atrioventricular node. The investigations concerning the specific activity of the atrioventricular tissue, and of the connected phenomena are not yet completed.

SPECIFICITY OF THE DESCRIBED PHENOMENA AND POSSIBILITY OF ARTEFACTS

It is unlikely that the described local action potentials of the sinus node and of the atrioventricular node are caused by artefacts, because of the following reasons:

1. The experiments are performed on intact hearts only.
2. The described specific local activity was, in all experiments, exclusively found in the region of the anatomic sinus node and atrioventricular node. In adjacent surrounding areas the simpler complexes of the common myocardium are found.
3. The very complicated pattern of the specific local activity in successive complexes is completely identical.
4. The specific differential sinus activity is most characteristic in the area where initial negativity is found in unipolar leads.
5. The specific differential atrioventricular complexes are found in the region where contact with the node or bundle is manifested by the occurrence of transient heart block, when too much pressure is applied by the needle electrode.

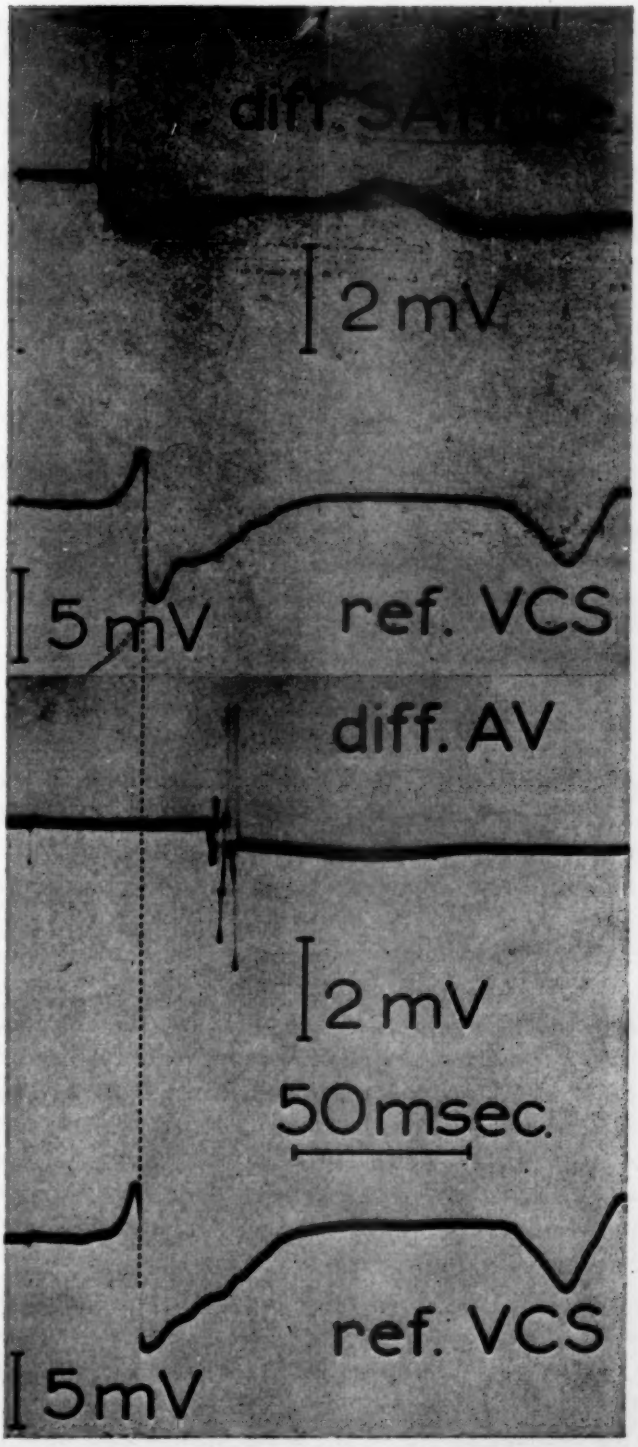

Fig. 9.—The lead named *diff. SA node* is a differential lead of the sinus node. The lead named *diff. AV node* is a differential lead of the atrioventricular node. The other two leads are unipolar reference leads of the vena cava superior. The differential complex of the sinus node falls at an earlier moment in the auricular cycle. The differential complex of the atrioventricular node appears at a much later moment. There is great similarity in the pattern of both differential nodal tissue complexes.

6. Anatomic verification of the areas where the specific and complicated differential complexes are found demonstrates that these leads are taken from the sinus node and atrioventricular node.

7. A study of the time relations shows that the beginning of the specific differential sinus complexes is the very first sign of activity of the auricles. The specific differential atrioventricular complexes are seen later in the heart cycle, approximately at the moment that the propagated activation front arrives in this region of the auricular septum.

8. The local action potentials of the sinus node and of the atrioventricular node are of a much lower voltage than the local action potentials elsewhere on the auricular myocardium in differential leads.

9. The duration of the differential complexes of the sinus node and of the atrioventricular node is strikingly larger than of the differential spikes of the common myocardium.

10. If auricular extrasystoles are made by electrical stimulation of the right auricular appendage, the complicated differential complexes of the sinus node region are substituted by a single auricular differential spike of higher voltage.

The next differential sinus complex again shows the similar complicated pattern of local sinus activity. This result excludes the possibility of an artefact, caused by our technique.

11. The similarity of the anatomic structure and of the local electrical phenomena of both nodal tissue areas could hardly be a coincidence.

12. The registration of the described, extremely fast phenomena of a very low voltage is only possible with a high fidelity apparatus as used in these experiments. These phenomena can not be found with the ordinary recording machines.

DISCUSSION

Sinus Node.—The specific complicated differential complexes of low voltage in the anatomic sinus node region are most characteristic in the small area of initial negativity.

The anatomic structure of the nodal tissues may be the cause of this phenomenon.

Somewhere in the capricious meshwork of specific nodal fibers separated by layers of connective tissue,[26] the depolarization begins. The activation passes through the meshwork of the sinus nodal tissue, but during the first milliseconds it does not spread out in the surrounding myocardium. The presence of what we believe to be insulating connective tissue layers may be of importance. The direction of the activation in this meshwork is changing continually, resulting in multiple fast deflections of low voltage in the differential lead. Many small offshoots of the sinus nodal tissue are in direct connection with the muscle fibers of the surrounding myocardium[26,28] and only by way of these offshoots is the common myocardium activated without further delay.

After activation of the surrounding myocardium, the local activity of the sinus node persists during 8 to 14 milliseconds. This is perhaps a kind of safety mechanism to assure the activation of the auricular myocardium surrounding the sinus node.

Perhaps this depolarization in the sinus node starts as a purely local phenomenon in only a few muscle fibers. It is also possible that this occurs in many places in the initial activated region of the sinus node. The latter possibility could contribute to the multiphasic differential complex, found in the pacemaker region of the heart.

The slow, potential fluctuations of very low voltage preceding the fast deflections of the differential sinus node complexes are very interesting. The form of those oscillations makes it improbable that the "prepotentials" are caused by depolarization of activated muscle fibers. A relation to the phenomenon of slow depolarization in the isolated Purkinje fibers, studied by Weidmann and Draper (1951),[23,24] and Trautwein[29] is possible. Eccles and Hoff (1934) presumed that a physiologic process precedes the initial activation of the sinus node. They postulated the existence of weak potential fluctuations preceding the fast potentials of the conducted impulse in the pacemaker region.[30]

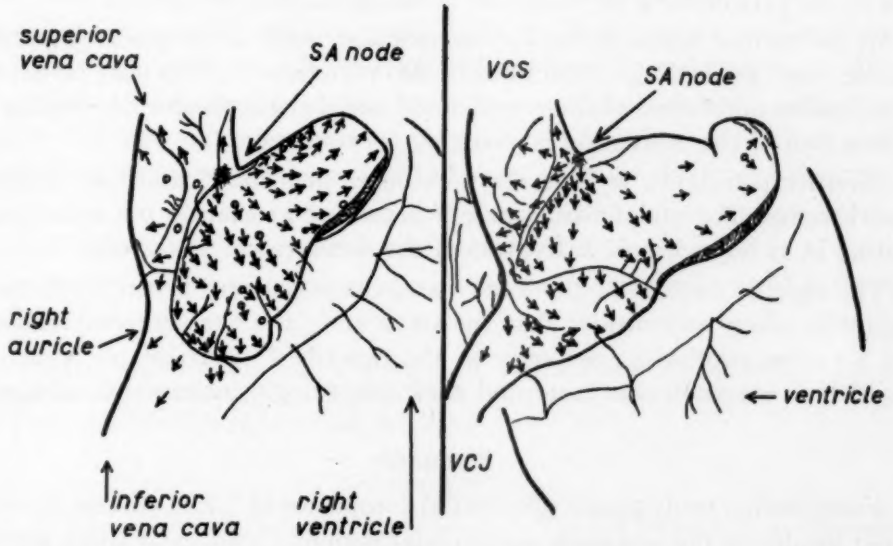

Fig. 10.—The direction of propagation of the activation wave was determined, with the aid of differential epicardial electrodes. The arrows indicate the direction of propagation in the investigated areas of the right auricles of two dogs. A small circle in the drawing means that no evident direction of propagation could be estimated. Note that the wave originating in the sinus node region does not spread exactly radially, but is slightly curved. The activation wave spreads along the thick muscular ridges of the auricular wall. This is the reason why the activation wave is not always propagated via the shortest possible route.

The initial negative complexes in the unipolar leads are complicated by many notches, as a result of the existence of a specific local sinus activity. The low voltage and the rapidity of this phenomenon are the reason why an exact study of the sinus activity can not be done with the commonly used apparatus.

The activation wave reaches the atrioventricular node by way of the auricular myocardium. Using differential leads, it is possible not only to determine the moment of activation, but also the direction of the activation wave on the auricular surface.

The activation wave travels with approximately constant speed. It spreads radially over the auricular surface, but is more or less deviated in the course of the thicker muscle ridges of the auricular wall. (Fig. 10.)

Never did we find any sign of the existence of a functionally specific conduction system in the auricular myocardium itself. Our experiments with intramural differential needle electrodes demonstrate the simultaneous activation of all layers of the auricular wall. In these experiments a small needle electrode is used with eight lead points which are all located in a 3 mm. part of the needle.[31,32] From this we must conclude that the activation wave travels in a tangential direction through the auricular myocardium.

Atrioventricular Node.—The atrioventricular nodal tissue also consists of a meshwork of specific nodal fibers, separated and surrounded by a lot of connective tissue.[27] The activation of this region is possible by many small offshoots of the nodal tissue, connecting directly with and changing into muscle fibers of the surrounding myocardium of the interauricular septum.[27,33]

In differential leads of the atrioventricular node, a complicated pattern of multiple, fast, low voltage deflections is also registered. This may be caused by the successive activation of the complicated nodal tissue meshwork, during which the direction of the activation is changing continuously.

Another possibility is that the previously mentioned multiple offshoots of the atrioventricular nodal tissue are not activated at exactly the same moment, resulting in an asynchronic activation of the nodal tissue meshwork.

The specific pattern of the local nodal tissue activity becomes all the more acceptable, when we consider that the sinus node and the atrioventricular node have a strong similarity, not only in the described electrical phenomena, but also in their anatomic structure and their physiologic tendency to automatism.

SUMMARY

Complicated multiphasic differential complexes of a low voltage are demonstrated locally in the anatomic sinus nodal region. This local sinus activity is, in differential leads, most characteristic in that part of the sinus node, where, in simultaneous unipolar leads, the initial negativity is found.

Pure initial negativity is seen only in a circumscript, very small area of the sinus node. The initial negative complexes are complicated by multiple fast deflections of a low voltage, and by notching of the descending limb.

A striking resemblance is seen with the unipolar complexes from the sinus node region in dogs, as published by Rijlant (1936).

With the help of a new technique, a similar complicated pattern of local activity is found in the atrioventricular node.

Complexes of this type have been seen in both nodal tissue areas and nowhere else in the auricular myocardium.

All experiments are performed on the intact heart of mongrel dogs.

We believe we have demonstrated the existence of an inherent local activity in the sinus node and in the atrioventricular node.

A theory is postulated concerning the origin and the conduction of the activation in the auricle of the dog.

SUMMARIO IN INTERLINGUA

Complicate complexos differential mutiphasic a basse voltage es demonstrate localmente in le region anatomic del nodo sinusal. Iste activitate sinusal local es, in derivationes differential, le plus characteristic in ille parte del nodo sinusal ubi, in derivationes unipolar simultanee, le negativitate initial es incontrate.

Pur negativitate initial es trovate solmente in un circumscriptissime e multo minute area del nodo sinusal. Le complexos negative initial es complicate per multiple deflexiones rapide de basse voltage e per le incisura del membro descendente.

Un frappante resimilantia es constatate con le complexos unipolar ab le region del nodo sinusal de canes, publicate per Rijlant in 1936.

Un nove technica ha rendite possibile le constatation de un similemente complicate configuration de activitate local in le nodo atrioventricular.

Complexos de iste genere esseva trovate in ambe areas nodal sed in nulle altere parte del myocardio auricular.

Omne le experimentos es executate in le corde intacte de canes bastarde.

Nos crede que nos ha demonstrate le existentia de un activitate local inherente in le nodo sinusal e in le nodo atrioventricular.

Es postulate un theoria concernente le origine e le conduction del activation in le auriculo del can.

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ALTERNATION OF CYCLE LENGTH IN PULSUS ALTERNANS

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IN PULSUS alternans the heart pumps larger and smaller quantities of blood in successive contractions of equal cycle length producing alternately strong and weak beats. Equality of cycle length between successive strong and weak beats has been stressed as a cardinal feature in the diagnosis, differentiating it from pseudo-alternans. While approximate identity of cycle length is the rule, successive intervals are seldom absolutely equal.

Wenckebach had observed that the weak beat of the couple can be regularly somewhat premature.[1] Slight prematurity of the weak beat may be identified in many published records of ventricular alternans.[2-4] The same phenomenon was noted in the records in six of eight patients with prolonged pulsus alternans studied at the hospital. All eight patients had organic heart disease, the etiology being hypertensive in three, arteriosclerotic coronary disease in three, rheumatic in one, and unknown in one.

METHODS

The present report is concerned with measurements of the cycle length in individuals with prolonged ventricular alternans, as well as in subjects with transient pulsus alternans which follows a premature contraction.

The electrocardiogram, heart sound, and femoral, carotid, or carotojugular pulse were recorded simultaneously. The patient was asked to hold his breath for a brief period without straining, usually permitting the recording of 20 to 40 consecutive beats.

Cycle length was measured from the peaks of the R or S waves in the electrocardiogram. Most records were made at a speed of 25 or 50 mm. per second. Viewed under magnification, they could be measured with an accuracy of 0.0025 to 0.0005 second.

Periodic alternation of cycle length in a succession of strong and weak beats may be detected by comparing the time interval between two beats and those immediately adjoining them.

A simple formula has been devised which reflects the presence and degree of prematurity in the alternate beats in a series independent of the overall progression in rate. In a series of alternating strong (S) and weak (W) beats SW_1S_{1-2}

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$W_2S_3W_3$, depicted in Table I, if there is no change in pulse rate within the series (Pattern A), the time intervals between successive beats will be identical and the middle interval (W_1S_2) will be equal in duration to the two adjoining ones. Thus, for Pattern A,

$$S_1W_1 = W_1S_2 = S_2W_2 = \frac{S_1W_1 + S_2W_2}{2}$$

$$\frac{S_1W_1 + S_2W_2}{2} - W_1S_2 = 0.$$

The latter equation will be equally true in a series of cycles that are changing at a constant rate either in decelerating (Pattern C) or accelerating (Pattern G) direction.

TABLE I. PATTERNS OF SUCCESSIVE STRONG AND WEAK BEATS SHOWING ISOCHRONICITY AND PERIODIC ALTERNATION OF CYCLE LENGTH SUPERIMPOSED UPON VARYING TRENDS (I.E., ACCELERATING, DECELERATING, OR UNCHANGING) IN PULSE RATE

PULSE RATE TREND WITHIN SERIES	PATTERN	CYCLE LENGTH IN 0.001 SEC. IN SUCCESSIVE STRONG AND WEAK BEATS										$\frac{S_1W_1 + S_2W_2}{2} - W_1S_2$ IN .001 SEC.	PREMATURITY OF WEAK BEAT
		S_1	W_1	S_2	W_2	S_3	W_3						
No change	A	600	=	600	=	600	=	600	=	600		0	None
	B	600	<	620	>	600	<	620	>	600		−20	Premature
Decelerating	C	600	<	620	<	640	<	660	<	680		0	None
	D	600	<	640	>	620	<	660	>	640		−30	Premature
	E	600	<	620	=	620	<	640	=	640		−10	Premature
	F	600	<	640	<	660	<	700	<	720		−10	Premature
Accelerating	G	600	>	580	>	560	>	540	>	520		0	None
	H	600	<	620	>	580	<	600	>	560		−30	Premature
	I	600	=	600	>	580	=	580	>	560		−10	Premature
	J	600	>	580	>	540	>	520	>	480		−10	Premature

If the weak beats are consistently premature, the cycle WS will be greater than the average of two adjoining SW cycles, and the difference between the two intervals will be expressed as a negative value. The magnitude of the negative value would reflect the degree of prematurity. Thus, if weak beats are premature,

$$W_1S_2 > \frac{S_1W_1 + S_2W_2}{2}$$

$$\frac{S_1W_1 + S_2W_2}{2} - W_1S_2 = \text{negative number.}$$

Prematurity of the weak beat is depicted in seven different patterns superimposed upon a basic rhythm which is decelerating (D,E,F), accelerating (H,I,J), or constant (B).

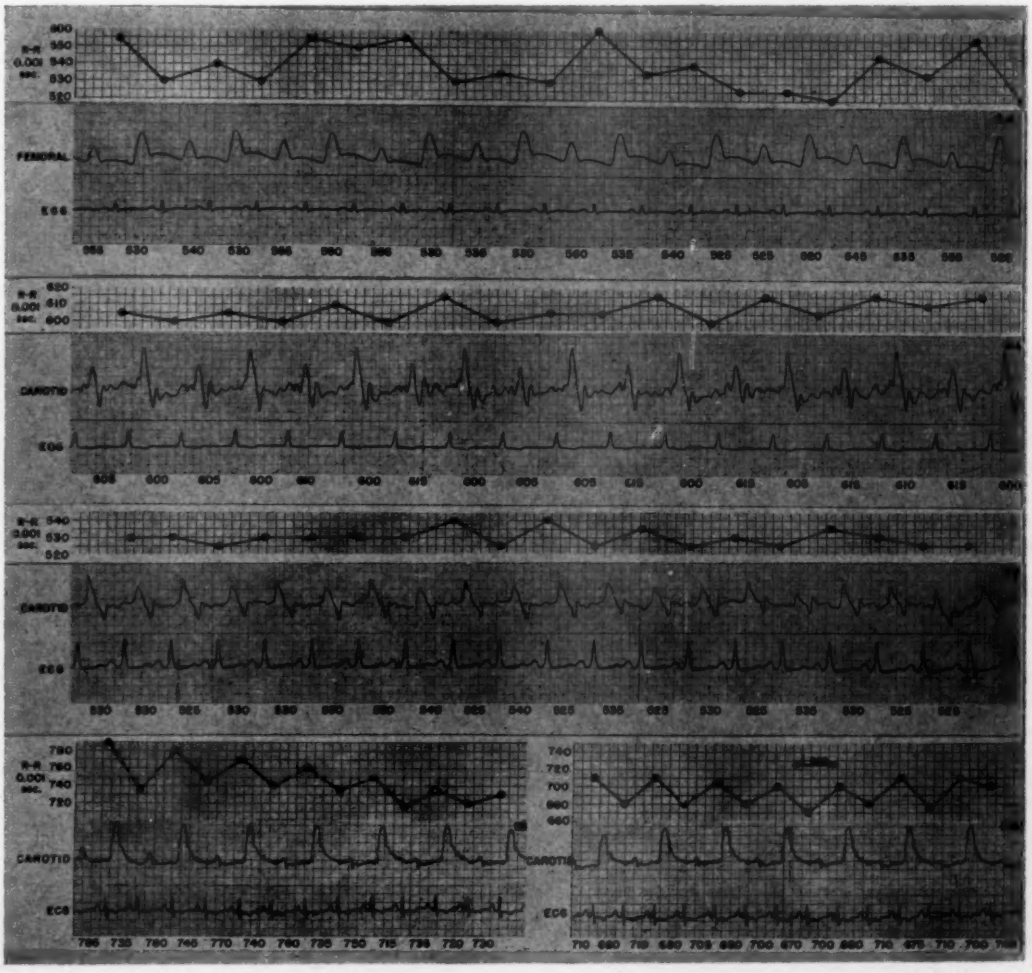

Fig. 1.—Alternation of cycle length in pulsus alternans in four cases. Upper three records made at a speed of 50 mm. per second. Figures denote cycle length in 0.001 second. ● = interval from weak to strong beat, and 0 = interval from strong to weak beat.

If the weak beats are consistently delayed, the interval WS will be less than the average of the two adjoining SW cycles and the difference between the two intervals should be a positive value. Thus if weak beats are delayed,

$$W_1S_2 < \frac{S_1W_1 + S_2W_2}{2}$$

$$\frac{S_1W_1 + S_2W_2}{2} - W_1S_2 = \text{positive number.}$$

This type of sequence could be depicted in seven patterns analogous to those described in Table I.

RESULTS

Table II summarizes the results in eight subjects with prolonged ventricular alternans. More than 800 couples were measured in thirty different records. The time interval between the weak and succeeding strong beat is compared with the intervals of the two adjoining beats between strong and weak impulses, employing the formula indicated above. The observations are tabulated on the basis of the time of arrival of the weak beat—i.e., "premature," "on time," or "delayed." In six instances there was a distinct tendency to prematurity of the weak beats varying in different individuals from 54 per cent to 88 per cent of all of the recorded couples. Weak beats that were delayed constituted a distinct minority, never exceeding 14 per cent of the total number. In two subjects (W.C. and C.S.) the distribution of intervals is consistent with random pattern.

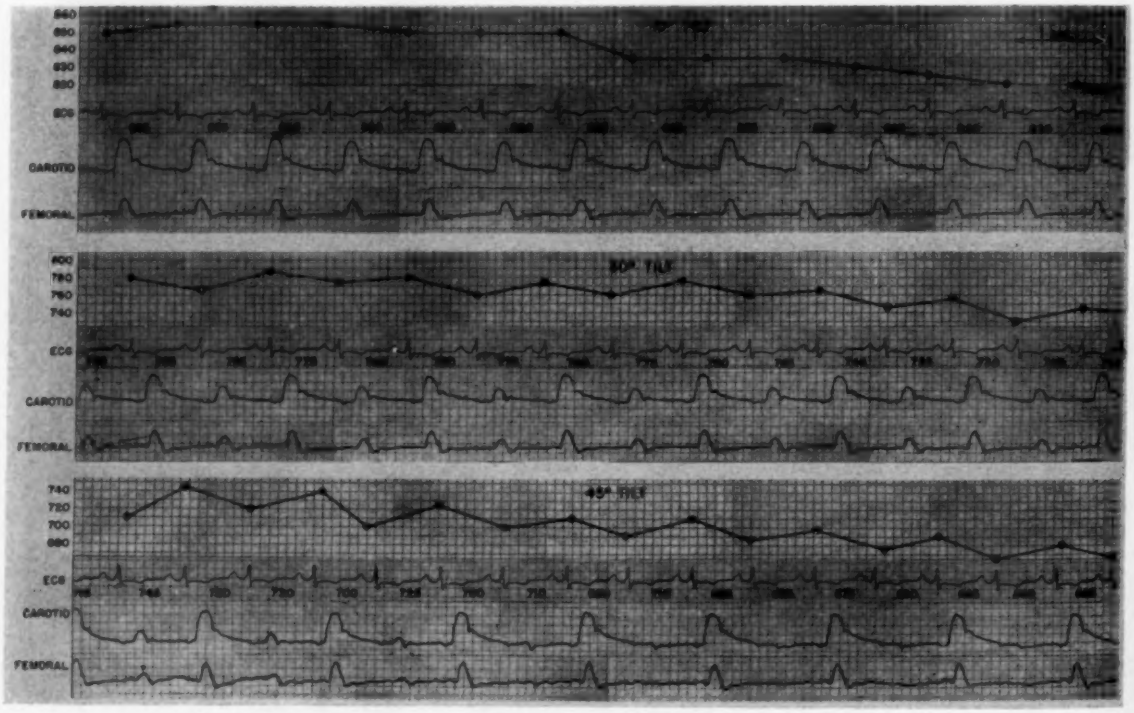

Fig. 2.—R. H. lying on tilt table. Simultaneous accentuation of mechanical alternans and alternation in cycle length on assuming semierect position. Figures denote cycle length in 0.001 second. • = interval from weak to strong beat, and 0 = interval from strong to weak beat.

The degree of prematurity in the six cases was generally on the order of 0.010 to 0.025 second, the extremes ranging between 0.0025 and 0.065 second, and the average being 0.017 second. A few typical records are shown in Figs. 1 and 2.

Four patients had ventricular alternation which could be enhanced or diminished by changes in body posture.[5] Pulsus alternans which was slight or absent in the recumbent position was exaggerated upon assuming the erect posture. When ventricular alternans was pronounced, there was also a tendency to alternation of cycle length in the direction of prematurity of the weak beat (Fig. 2).

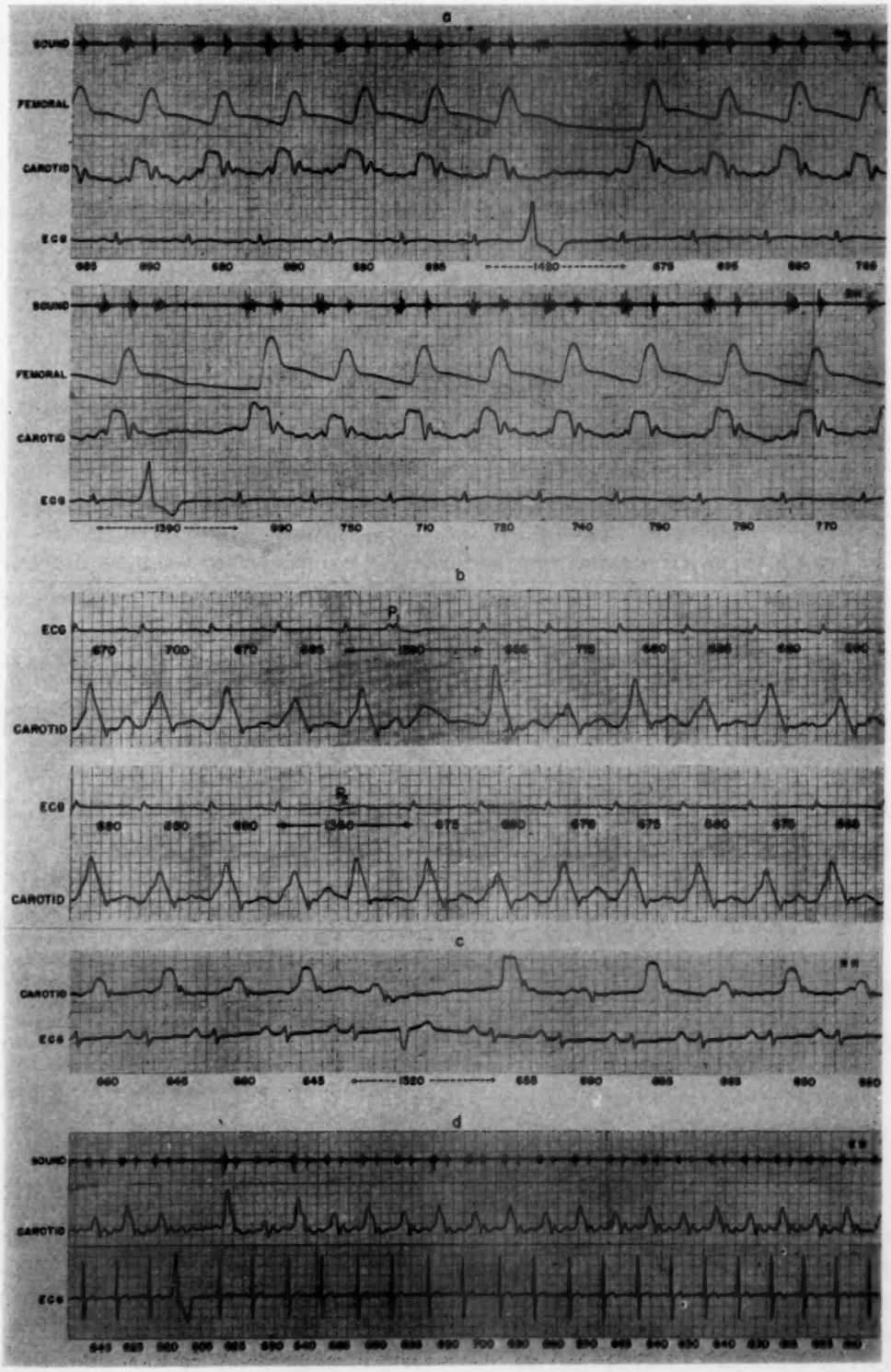

Fig. 3.—Pulsus alternans following premature beats. Figures denote cycle length in 0.001 sec.

a. Upper 2 records are continuous. Premature beats do not produce effective pulse or second heart sound. Pulsus alternans is transient.

b. Middle two records are continuous. First premature beat (P_1) replaces weak beat and is followed by transient increase in severity of mechanical alternation. Second premature beat (P_2) replaces strong beat and results in a reversal in sequence of strong and weak contractions. In both instances the shortened cycles precede the weak beats.

c and *d*. Transient accentuation of mechanical and temporal alternation following P.V.C.

TABLE II. CYCLE LENGTH OF WEAK TO STRONG BEATS IN RELATION TO ADJOINING BEATS IN PATIENTS IN ERECT POSTURE WITH PULSUS ALTERNANS

PATIENTS	NUMBER OF COUPLES MEASURED	AVERAGE CYCLE LENGTH 0.001 SEC.	WEAK BEAT—PREMATURE $W_1S_2 > \frac{S_1W_1 + S_2W_2}{2}$				WEAK BEAT—ON TIME $W_1S_2 = \frac{S_1W_1 + S_2W_2}{2}$		WEAK BEAT—DELAYED $W_1S_2 < \frac{S_1W_1 + S_2W_2}{2}$			
			NO.	%	RANGE	(MEAN)	NO.	%	NO.	%	RANGE	(MEAN)
					0.001 SEC.						0.001 SEC.	
E.B.	204	540	165	81	2.5–65	(27)	20	10	19	9	2.5–15	(9)
R.H.	326	650	287	88	2.5–25	(15)	24	7	15	5	2.5–10	(9)
J.W.	78	700	60	77	2.5–30	(23)	11	14	7	9	2.5–15	(8)
B.Y.	35	500	22	63	2.5–15	(8)	9	26	4	11	2.5–12.5	(7)
F.J.	140	580	75	54	2.5–15	(12)	45	32	20	14	2.5–12.5	(9)
W.D.	12	560	8	67	2.5–10	(5)	4	33	0	0	—	—
W.C.	16	690	7	44	2.5–25	(6)	4	25	5	31	2.5–45	(4)
C.S.	30	710	8	27	2.5–10	(5)	14	47	8	27	2.5–10	(6)

TABLE III. CYCLE LENGTHS OF SUCCESSIVE BEATS IN RELATION TO ADJOINING BEATS IN SUBJECTS WITH MINIMAL OR NO PULSUS ALTERNANS IN THE RECUMBENT POSITION

PATIENT	NUMBER OF COUPLES MEASURED	EVEN-NUMBERED BEAT PREMATURE				EVEN-NUMBERED BEAT ON TIME		EVEN-NUMBERED BEAT DELAYED			
		NO.	%	RANGE	(MEAN)	NO.	%	NO.	%	RANGE	(MEAN)
				0.001 SEC.						0.001 SEC.	
E.B.	70	26	37	2.5–20	(14)	10	14	34	49	2.5–30	(11)
R.H.	56	25	45	2.5–25	(20)	6	10	25	45	2.5–15	(9)
J.W.	35	10	29	2.5–10	(6)	11	31	14	40	2.5–5	(6)
B.Y.	28	13	47	2.5–12.5	(5)	3	10	12	43	2.5–15	(6)

In the horizontal position, when ventricular alternans was slight or absent, the pattern of consecutive R-R intervals showed no such tendency, the succession of cycle intervals falling in random distribution (Table III).

PULSUS ALTERNANS FOLLOWING ECTOPIC BEATS

Ectopic beats occurring in either normal or diseased hearts are frequently followed by transient ventricular alternation. This phenomenon is usually noted in the first 4 or 6 beats following the ectopic beat, and longer if severe organic heart disease exists (Fig. 3). If pulsus alternans in a mild form was present prior to appearance of the ectopic beat, the degree of ventricular alternation was temporarily exaggerated (Fig. 3,*c* and *d*).

In five subjects spontaneous ectopic beats were recorded on different occasions. Three of these individuals had exhibited pulsus alternans at some time, and two patients had no ventricular alternation except for a short interval following the premature beat. In thirty-nine instances the records were suitable for measurement. In almost all of them pulsus alternans was present for the first 4 postextrasystolic beats, and in half of them for the first 8 beats. After the sixth beat pulsus alternans had either disappeared or was very mild. The observations are summarized in Table IV.

TABLE IV. CYCLE LENGTH OF WEAK BEAT IN RELATION TO ADJOINING BEATS IN PULSUS ALTERNANS FOLLOWING SPONTANEOUS ECTOPIC BEATS. THIRTY-NINE INSTANCES IN FIVE PATIENTS. THE ODD-NUMBERED BEATS ARE STRONG—THE EVEN-NUMBERED ARE WEAK

	POSTEXTRASYSTOLIC BEATS			
	1 to 3	3 to 5	5 to 7	7 to 9
Number (%) of couples showing pulsus alternans	39 (100%)	38 (97%)	25 (64%)	20 (51%)
Weak beat premature				
Number (%)	36 (92%)	31 (82%)	17 (68%)	8 (40%)
Range in 0.001 sec.	2.5–85	2.5–60	2.5–50	2.5–40
Mean in 0.001 sec.	32	17	17	17
Weak beat on time				
Number (%)	2 (5%)	1 (2%)	2 (8%)	4 (20%)
Weak beat delayed				
Number (%)	1 (3%)	6 (16%)	6 (24%)	8 (40%)
Range in 0.001 sec.	20	2.5–15	2.5–10	10–25
Mean in 0.001 sec.	20	7	6	12

It may be seen that there is a definite correlation between degree of mechanical alternation on the one hand, and incidence of prematurity of the weak beat on the other. The incidence of relative prematurity in the successive even-numbered or weak beats (2, 4, 6, and 8) is, respectively, 92 per cent, 82 per cent, 68 per cent, and 40 per cent. The degree of prematurity of the weak beat was greater in the first couple (average 0.032 second) than in the subsequent couple (average 0.017 second).

When the premature impulse replaced the weak beat, the sequence of strong and weak contractions which followed remained unchanged. In a few instances the premature beat replaced the strong beat, resulting in a reversal of the sequence (Fig. 3,*b*).

DISCUSSION

Any rhythm in which successive beats alternate in cycle length as well as in strength must be differentiated from pseudo-alternans, due to premature beats of ectopic origin, sinoauricular block, sinus arrhythmia, and phasic respiratory effects. Respiratory effects may be excluded at once since this phenomenon was recorded during breath-holding. The identical configuration of electrocardiographic tracings without the slightest variation in normally appearing P waves or P-R intervals speaks against alternating premature beats of ectopic origin. Premature beats of sinus origin can occur, and a form of bigeminy due to this type of arrhythmia has been described.[6,7] The incidence of this arrhythmia appears to be extremely rare. In the four or five credible instances recorded, the differences in length between cycles of normal beats and those containing premature beats varied between 0.18 and 0.32 second.[8] These degrees of prematurity are about ten times those observed in the patients of the present report, in whom the premature beat fell about 0.02 or 0.03 second short of the expected arrival time. The theoretical possibility exists of recurring phasic, very late premature beats arising within the sinus node. Actually the incidence of premature beats arising in different sites varies inversely with the rate of spontaneous impluse formation, being greatest in the ventricle and least in the sinus node. It would be highly unusual to find such a high incidence of this rare arrhythmia without evidence of ectopic stimulation in the auricle.

Another possibility to be considered is sinoauricular block due either to nonconducted sinus beats occurring every third or fourth beat, or to alternation in the sinoauricular conduction time. The first possibility would be expected to result in much greater variation in cycle length than those observed in these patients. The second possibility cannot be excluded, but is not likely in view of the tendency for the alternation in cycle length to disappear with recumbency.

The association of mechanical alternation with alternation in cycle length evokes speculation as to the existence of a cause and effect relationship between the two phenomena. Three possibilities suggest themselves. Mechanical alternation may be either the cause or the result of alternation in cycle length, or else the two phenomena may not be casually related to each other but to some common factor in neuromuscular activity of the heart, such as an alternating type of conduction block in the sinus and ventricle. With respect to the last possibility, it is difficult to conceive of a block in conduction that would be affected rapidly by changes in body position. A hypothetical conduction block would have to be in opposite phase in the sinus and ventricle to account for the sequence of a short R-R interval followed by defection of ventricular contraction.

Many investigators have stressed the effect of hemodynamic factors in the mechanism of ventricular alternans.[1,9,10] Although prolonged pulsus alternans involves, primarily, an impairment in contracting power of the myocardium,

alterations in ventricular filling and diastolic distention can play a secondary part in the intensity of alternation.

The influence of diminished diastolic filling may be invoked at first glance as the simplest explanation for the observation that the weak beat follows the shorter cycle and the strong beat follows the longer cycle. A given degree of curtailment of the length of the cycle would be expected to have effects on ventricular filling which vary directly with the heart rate. The reasons are twofold. At rapid heart rates the ventricular filling rate is rapid thoughout and does not taper off toward the end.[11] As the heart rate increases ventricular diastole occupies progessively smaller fractions of the total cardiac cycle. Using Ashworth's tables for duration of systole and diastole at different heart rates, it may be calculated that a shortening of 0.02 second in the cardiac cycle, accomplished exclusively at the expense of diastole, will result at heart rates of 80 and 150 per minute in a maximum reduction of ventricular diastolic time of 4.9 per cent and 13.5 per cent respectively. At rapid rates this degree of curtailing of diastolic filling time may significantly reduce the strength of the ensuing ventricular ejection.

It is of interest in this connection that, in the dog with an artificially driven heart, Wiggers was able to induce ventricular alternation following premature beats only under conditions of heart rates above 140 per minute.[9] In patients without organic heart disease pulsus alternans occurs transiently, following a premature beat, or for prolonged periods as an accompaniment of marked tachycardia, usually of ectopic origin. These varieties of ventricular alternans are benign. Hemodynamic rather than myogenic mechanism are probably primarily concerned in their production.

In the patients in this study the heart rates were usually above normal and the cycles culminating in the weak beats were shortened by intervals of 0.005 to 0.027 second, the mean being 0.017 second. The greatest degree of prematurity of the weak beat occurred in subject E.B., at a heart rate of 110 per minute, and averaged 0.027 second. Assuming a constant rate of ventricular filling (an assumption that is not warranted), this degree of prematurity would account for a maximum possible diastolic filling deficit of about 11 per cent. This is based on the assumption, which probably is not valid, that the entire reduction in cycle length is accomplished at the expense of ventricular diastole. Similar calculations for the other five subjects in whom prematurity of the weak beat was observed indicates maximum possible deficits in duration of diastole to be 4.0, 6.2, 4.2, 4.0, and 1.8 per cent of the expected normal periods. Except for subject E.B., reductions of this minute degree can hardly be credited with an important role in producing a weak beat, particularly at heart rates under 100 per minute in which the rate of ventricular diastolic filling is greatly reduced toward the latter portion of relaxation. Certainly the change from a barely attenuated beat in the recumbent posture to an almost imperceptible weak beat in the same individual lying at a 45 degree incline (Fig. 2) cannot be ascribed to the concomitant slight change in rate and alternation in the length of the cycles.

An alternative hypothesis is proposed; namely, that the alternation in cycle length is not the cause but the consequence of alternation in strength of the preceding ventricular systole. Two mechanisms may be involved here: (1) direct mechanical action on the overlying sinus pacemaker, (2) reflex vagal effects mediated by way of the aortic and carotid pressoreceptors. Several investigators have reported that stretching or deformation of auricular muscle accelerates the rate of impluse formation.[12,13] This mechanism has been invoked by Perrin[14] to explain certain cases of coupling with bigeminal rhythm, and by Rosenbaum and Lepeschkin[15] to account for the accelerating action of ventricular systole on auricular rhythm in auriculoventricular block. A strong ventricular beat, vigorously displacing the base of the attached auricle, would be expected to have an immediate effect in accelerating the rate of stimulus formation and in shortening the next cycle. A strong beat would also stimulate the arterial pressoreceptors and slow the heart rate. This slowing action and the lengthening of the R-R interval in the electrocardiogram does not become manifest on the first, but on the second succeeding beat. The lag is due to the lapse of time for completion of the reflex pathway. The two longest components of this pathway are the interval from beginning to the peak of systolic ejection and the period of latency in the sinus node. In a recent discussion of this aspect of the reflex pathway, it has been estimated that, in the dog, the latent period from beginning of stimulation of the arterial pressoreceptors to the earliest effect on P-P interval was about 0.4 second and to the maxium effect, 0.9 second or longer. Latent periods of this magnitude, measured from the point of the peak of the aortic pressure or volume curve, would have the greatest influence on the P-P or R-R interval immediately following the next beat.

In line with this hypothesis, the sequence of events is as follows: A strong beat stimulates the pacemaker by mechanical distortion, thereby effecting immediate shortening of the next cycle which culminates in a weak beat; at the same time, at the peak of the systolic ejection of the strong beat, a reflex is initiated which results in lengthening of the cycle. Because of the latent period, the latter effect does not become manifest until the second succeeding beat, which is again strong. Changes in the opposite direction accompany the weak beat. The end result is a succession of alternate strong and weak beats, the former being followed by a short cycle, and the latter by a longer cycle. The weak beat appears to fall somewhat prematurely in comparison with the two adjoining beats.

If the above hypothesis is correct, one would expect that differences in degree of mechanical alternation of the pulse volume would be reflected in corresponding variation in the magnitude of aternation in cycle length. A general tendency in this direction was noted, although the levels of blood pressure were not recorded directly, but estimated in the amplitude of the pulse tracings. The correlation is observed especially in the individuals in whom intensity of ventricular alternation was varied at will by postural changes, and in subjects with spontaneous premature beats. In the latter, the vigor of the beat, as reflected in the amplitude of the pulse wave, was greatest in the first postextrasystolic beat, and least in the second. The subsequent alternately strong and weak

beat either disappeared entirely after the fourth or fifth beat or returned to the pattern prevailing prior to the appearance of the premature beat.

The heart rate is never absolutely constant, even at rest. This is not surprising in view of the many different factors which normally affect the rate of impluse formation. Neurogenic impulses from the lungs, viscera, basal ganglia, and higher cerebral centers impinge constantly on the cardiac pacemaker, stimulating or depressing it as the case may be. The simultaneous operation of these physiologic processes may augment or counteract the effects of stimuli which cause alternation in cycle length in pulsus alternans. In some cycles the net effect may be an unusual degree of shortening, and in others, the reverse. This may account for the fact that a few cycles terminating in weak beats were premature by as much as 0.065 second and others (less than 9 per cent) were actually delayed as long as 0.01 or 0.015 second.

SUMMARY

In six out of eight instances mechanical ventricular alternans was accompanied by minute alternation in cycle length.

Similar changes in cycle length were observed in the transient pulsus alternans which follows a premature contraction.

The strong beats are followed by shortened cycles and the weak beats by longer cycles, the differences being usually about 0.01 to 0.03 second in duration.

In four subjects in whom pulsus alternans was accentuated in the erect posture, both the mechanical and temporal types of alternation changed in a concordant direction, both tending to disappear in the recumbent position.

The changes in cycle length are considered in most instances to be the consequence rather than the cause of alternation in strength of the contractions. The mechanism is believed to involve two asynchronous effects of a single strong or weak beat: (1) An immediate effect on the first succeeding cycle by alternation in direct mechanical distortion and stimulation of the pacemaker; (2) Delayed pressoreceptor reflex action which, because of the latent period, does not become manifest until the second cycle.

In very rapid heart rates, slight alternations in cycle length may contribute to the development or severity of mechanical alternation.

SUMMARIO IN INTERLINGUA

Exacte mesurationes revelava un alte frequentia de minute inequalitates del longor de cyclo in pulsos successive de certe patientes con pulso alternante. Le cyclo que precedeva le pulso de fortia reducite esseva regularmente distinguite per un leve reduction de longor in comparation con le adjacente cyclos a termination in pulsos forte. Un simile alternation del longor cyclic esseva observate in le transiente pulso alternante ventricular que seque un pulso prematur e in le pulso alternante que varia con le postura del subjecto.

Le autor discute le mechanismos que es possibilemente involvite in iste phenomeno. Le hypothese le plus plausibile es que le alternation del longor cyclic es le resultato plus tosto que le causa del alternantia mechanic.

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THE NORMAL VECTORCARDIOGRAM. I

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INTRODUCTION

THIS study is concerned with a description of the normal vectorcardiogram. It was undertaken to supplement the morphologic descriptions of planar vectorcardiograms[1-10] and to obtain measurements of the QRSsÊ loop. In addition the S-T junction (J) was studied, and measurements of the TsÊ loop were made. The latter were incomplete, since detailed analysis of the TsÊ loop requires different timing interruption than that used in collecting data for this study.[1] The relationship of the QRS to the T vectors is presented. The PsÊ loop was not studied.[18]

MATERIALS AND METHODS

Vectorcardiograms and electrocardiograms were obtained on 100 healthy patients with normal hearts. There were fourteen women and eighty-six men with age distribution shown in Table I. More than half of the subjects were medical students and house staff between ages 20 and 30. Infants and children were excluded.[11] All were questioned carefully and examined for evidence of cardiovascular disease. P-A and lateral teleorentgenograms of the chest were available on all subjects, and fluoroscopy was done on a few individuals.

TABLE I. AGE DISTRIBUTION OF 100 NORMAL SUBJECTS

Age	19	20–29	30–39	40–49	50–59	60–69	74
Number	1	63	12	13	7	3	1

Electrocardiograms, with one or two exceptions, were taken on a Sanborn Poly-Viso direct-writer four-channel instrument with Lead I as common reference. The standard and unipolar limb leads, unipolar precordial Leads V_6R to V_6, and Leads V_E (ensiform) and V_L (angle of Louis) were obtained. V_E posterior (V_EP) and V_L posterior V_LP) were also obtained by placing the exploring electrode on the spine at the same level used for the anterior Leads V_E and V_L.

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Horizontal (right-to-left), sagittal (anterior-to-posterior), and vertical (superior-to-inferior) leads—designated X, Y, and Z^1 (Leads A, B, and C of Grishman[9]) —were registered. Subjects with electrocardiographic abnormalities were excluded from this study.

Horizontal, sagittal, and frontal planar projections were obtained using the orthogonal reference system of Duchosal,[5] but with positive polarity.[1] No adjustment in circuit sensitivity was made for unequal vertical[9] and anterior-posterior dimensions of the reference frame. For purposes of comparison, three planar projections were obtained in each case, using the modified Cube system adopted by Grishman and associates,[9] but only the vectorcardiograms taken with the double Cube system of Duchosal have been analyzed in detail. The observations that follow refer to the Duchosal system unless otherwise stated.

Electrodes were placed at the following points: spine of the right scapula in the posterior axillary line, right anterior and posterior axillary line at the level of of the iliac crest, and left posterior axillary line at the level of the iliac crest. For sake of easy identification, the lower borders of the three inferior electrodes were placed just above the crest of the ilium. When the Cube system was used, the inferior electrodes were placed one or two interspinal spaces higher.

A Dumont oscilloscope type 304 A was used in conjunction with two Tektronix type 122 preamplifiers. One of the desirable features of this preamplifier is its high impedance input, namely 2 megohms; this attribute tends to minimize distortion produced by variations in skin resistance at the electrodes.[10] The lower limit of frequency response of the preamplifiers was set at 0.2 cycle per second, the upper limit at 150 cycles per second. This frequency response is adequate, considering the present state of our knowledge.[9,10,15]

Tektronix type 122 amplifier was used for the X axis in preference to the X amplifier of the Dumont oscilloscope. This permitted operation of the preamplifiers at 100 amplification without sacrificing high gain. Since both X and Y amplifiers were being run at relatively low frequency levels, it may be safely assumed that their response gave equal deflections with the same scale factor in the X and Y axes. The above combination of preamplifier and amplifier stages comprises resistance-coupled (RC) and direct-coupled (DC) circuits, the most preferable design at this time.[10]

The spot on the oscilloscope screen is very small, a desired technicality in vectorcardiography.

The additional apparatus included a Dumont oscilloscope camera type 296 with attached hood. The proper moment of exposure was attained by manual means. With experience one is able to dissect the loop by eye. Satisfactory photographs of the initial QRS forces can be obtained by quickly opening and closing the camera shutter at the proper instant. This technique was suggested by Duchosal[5] to eliminate P, T, and late QRS vectors, and obviates the need for intricate timing devices.[10,12]

The loops were interrupted by a signal from an electric tuning fork 400 times per second, giving time markings of 0.0025 second. A tear-drop image, indicating direction of inscription of the trace, was superimposed by a decade of condensers parallel with biased crystal diodes.

All units were grounded to a common point, and wires carrying alternating current were of the shielded type and grounded to avoid null point distortion.

The apparatus was mounted on a cart measuring 2 by 3 by 2¼ feet, providing a relatively simple portable outfit.

Eastman Kodak XX 35 mm. film (100-foot spools) was rolled into thirty-five exposure packets. When using such sensitive film, it is desirable to adjust the intensity of the oscilloscope spot so that a slight halo is seen in complete darkness. This furnishes a photograph which is sufficiently dark yet without obliteration of the initial QRS forces by the halo about the null point.

It is important that electrode paste be rubbed into the skin to the point of evoking rubor. The best graphs are obtained if the patient holds his breath in neutral position. These two factors, unless adequately controlled, will result in "AC" interference and distortion of the loop due to wandering of the null point. Inasmuch as breathing was regulated, we did not concern ourselves with gross deviations resulting from respiratory excursions.[9]

It has been stated that, "Vector quantities located near the isoelectric point will usually be obscured by the movement of the cathode ray beam near this point."[2] We believe, however, that use of the above equipment, and adherence to the techniques and precautions advocated usually obviate the difficulty caused by noises in amplifier circuits, skin currents, extrinsic alternating currents, and currents from skeletal muscle contraction. Furthermore, accuracy of timing is made possible by the aforementioned adjustment of intensity of the fluorescent spot which prevents the time interruptions from running into each other.

Vectorcardiograms were studied by placing the 35 mm. film on the magnifying screen of a Remington-Rand Viewing Box Type F-71. Measurements were made on this screen and adjusted in accordance with the circuit sensitivity (standardization) in each case. Nine and one-half inches on the viewer was equal to four inches on the oscilloscope screen; the equivalent voltage was calculated according to the standardization.

RESULTS

The terms right, left, anterior, posterior, superior, and inferior refer to the patient and are used in the same way be Grishman and others.[1,3,9]

Polarity and general form and direction of inscription of the loop were essentially the same in vectorcardiograms taken with the Duchosal and Cube reference system, but the magnitudes differed. The Duchosal loops were greater in their vertical and smaller in their anterior-posterior dimensions. The right-to-left dimensions were often greater by the Cube method.

The QRSsÊ loop was arbitrarily divided into initial forces, body, and terminal appendage. The initial forces are defined as forces at the beginning of the QRS loop which are oriented to the right and/or superior to zero. The terminal appendage is arbitrarily taken to mean the forces at the end of the QRS loop which are oriented to the right and/or superiorly. The initial forces and terminal appendage correspond in a general way to Q or S waves, respectively, and are of great diagnostic value. The initial forces were invariably oriented anteriorly, the appendage posteriorly, or partly posteriorly and partly anteriorly. Occa-

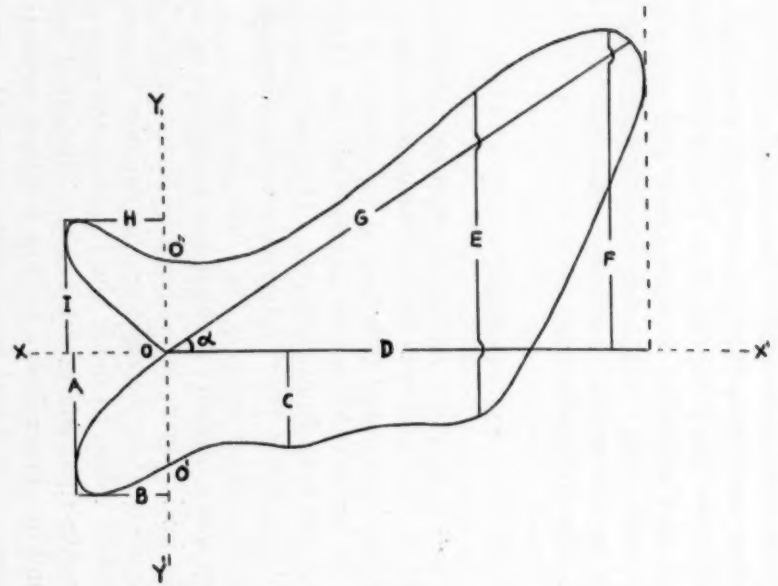


Fig. 1.

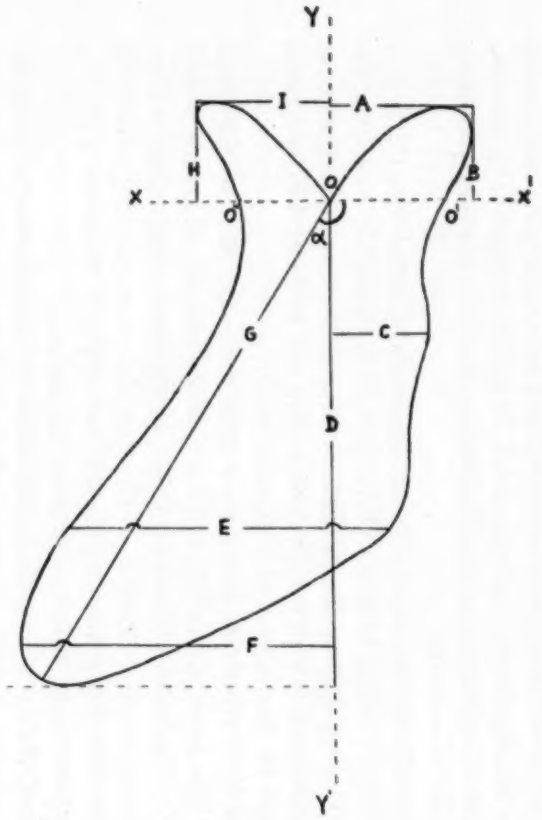


Fig. 2.

Fig. 1.—Horizontal projection: O at the point of intersection of XX' and YY' equals the point of origin of the cardiac vector. G equals maximal vector. Long axis equals angle subtended by maximal vector (G) and XX'. Initial forces equal the trace starting at O and ending at O'. Body equals the trace starting at O' and ending at O''. Terminal appendage equals the trace starting at O'' and ending at O.

Perpendicular projections of maximal dimensions of: Initial forces: A = anterior, B = right; Body: C = anterior, D = left, E = width, F = posterior; Terminal appendage: H = rightward, I = posterior.

Fig. 2.—Sagittal projection: O at the point of intersection of XX' and YY' equals the point of origin of the cardiac vector. G equals the maximal vector. Long axis equals angle subtended by maximal vector (G) and XX'. Initial forces equal the trace starting at O and ending at O'. Body equals the trace starting at O' and ending at O''. Terminal appendage equals the trace starting at O'' and ending at O.

Perpendicular projections of maximal dimensions of: Initial forces: A = anterior, B = superior; Body: C = anterior, D = inferior, E = width, F = posterior; Terminal appendage: H = superior, I = posterior.

sionally the final vectors of the appendage were directed inferiorly and to the left. The body of the QRSsÊ loop usually appeared as a hemioval projection in the horizontal and sagittal planes, and was composed of a centrifugal and centripetal limb joining the initial forces and the appendage. The body had a leftward and inferior position, and usually was oriented both anteriorly and posteriorly, rarely entirely anteriorly. It was divided equally into three portions in the horizontal and sagittal projections: proximal (contiguous to zero point), middle, and distal.

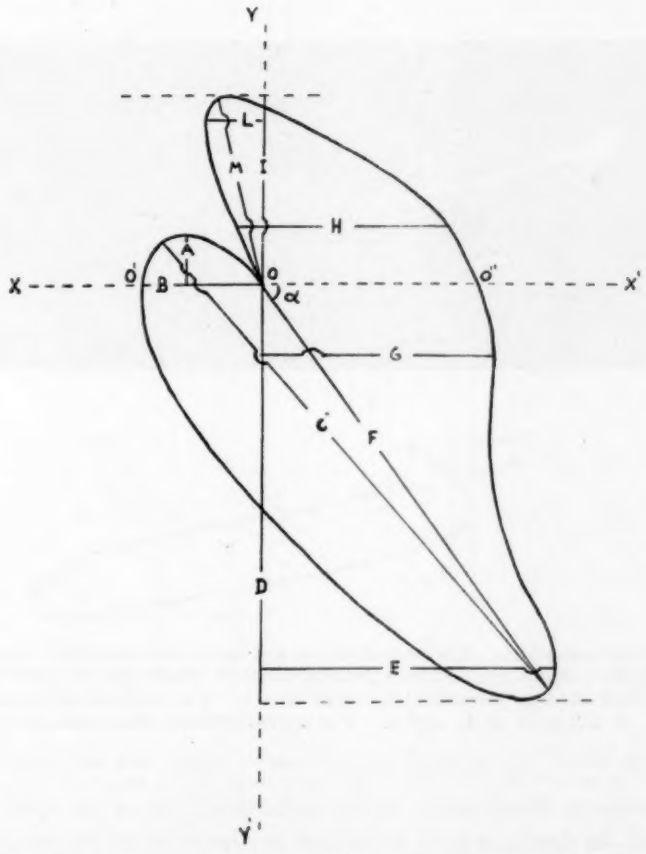


Fig. 3.—Frontal projection: *O* at the point of intersection of *XX'* and *YY'*, equals the point of origin of the cardiac vector, *F* equals the maximal vector. Long axis equals angle α subtended by maximal vector (*B*) and *XX'*. Initial forces equal the trace starting at *O* and ending at *O'*. Body equals the trace starting at *O'* and ending at *O''*. Terminal appendage equals the trace starting at *O''* and ending at *O*.

Perpendicular projections of maximal dimensions of: Initial forces: *A* = superior, *B* = right; Body: *D* = inferior, *E* = left, *G* = width; Terminal appendage: *H* = width, *L* = right, *I* = superior; Largest vector: *C* = sum of initial forces and body (measured only if initial forces went superior), *F* = body (maximal vector in normal subject), *M* = appendage.

The right-left, anterior-posterior, and superior-inferior displacements of the maximal vectors in the horizontal, sagittal, and frontal planes were obtained by dropping perpendiculars from the heads of these vectors to the horizontal or vertical lines drawn through zero, as shown in Figs. 1, 2, and 3. The actual

lengths of the maximal vectors in the frontal plane were also measured in addition to the right-to-left and superior-to-inferior displacement, as shown in Fig. 3.

QRS LOOP

Horizontal Plane.—The loops were smooth, slightly flattened ovals with a variable amount of posterior bulging terminally, and a maximal duration of 0.095 second (38 interruptions). The early and late vectors, with few exceptions, were more slowly inscribed than the rest of the loop, the former up to 25 per cent,

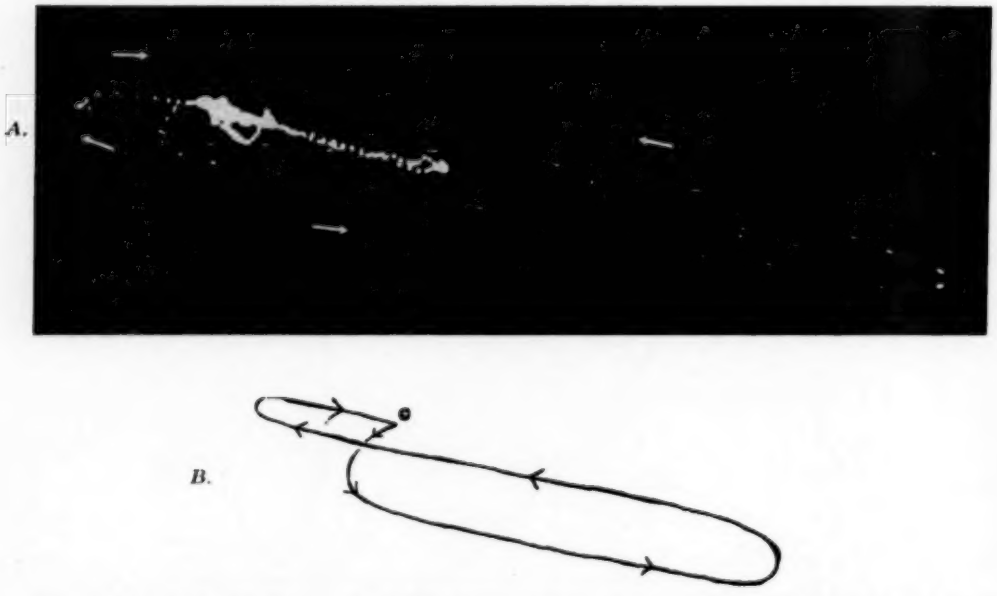
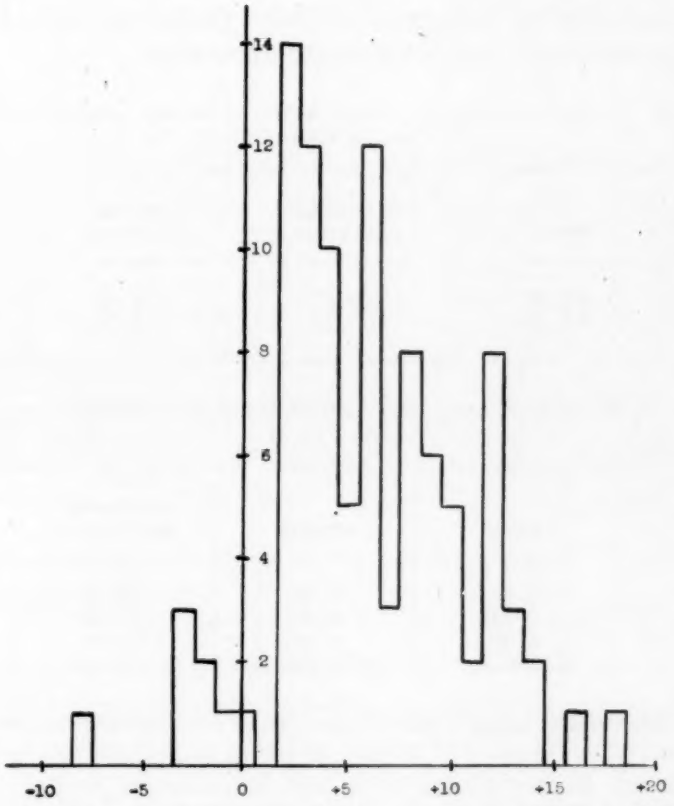


Fig. 4.—*A*, Horizontal plane. QRS initial forces and body are completely anterior to zero. Only the early portion of the terminal appendage is anterior to zero. Note that the latter portion of the body is posterior to the most anterior portion of the initial forces. The terminal appendage is clockwisely inscribed. (See *B*.) *B*, Diagram of *A*. QRS. The arrows indicate the sequence of inscription.

the latter as much as 40 per cent of the total duration of the QRS. At times the distal portion of the body, where a change in direction of forces occurred, showed some slow inscription. The entire loop, except for the terminal appendage in certain instances, was counterclockwisely inscribed. Sudden gross changes (notches) in direction did not occur. In some cases terminal appendages, with rightward and entirely posterior forces, presented a figure-of-eight configuration in which the most rightward portion of the appendage was very narrow and clockwisely inscribed. In six vectorcardiograms the initial forces, the body, and all but the end of the terminal appendage were entirely anterior to the null point; the terminal appendage in all six cases was wholly or partly clockwisely inscribed, or the efferent and afferent limbs were superimposed (Fig. 4).

The long axis is defined as the angle subtended by a horizontal line drawn through the zero point and the maximal vector. The angle is zero degrees when the maximal vector coincides with the horizontal line, positive when it

is anteriorly, and negative when posteriorly displaced. The angles varied from plus 18 to minus 8, compared to plus 14, and minus 19 with the Cube system (Table II). Nevertheless, the angle was not invariably more positive with the Duchosal than with the Cube system. The long axes for the entire series are shown in Graph I.



Graph 1.—The QRS long axis (angle) in the horizontal plane of 100 normal patients, obtained by the Duchosal method. Ordinates equal number of individuals, abcissae, the long axes in degrees.

Initial Forces.—Initial rightward forces were present in all subjects except five; in two of the latter, however, rightward initial forces were evident in the frontal plane. The initial forces were anteriorly oriented in their entirety. They formed a hemioval, or when very small, displayed superimposition of the efferent and afferant limbs. Anterior displacement of the efferent limb was minimal, but that of the afferent limb considerably greater. Table III shows the measurements of the initial forces in the horizontal plane.

Body.—As already stated, the body of the loop had a hemioval configuration in the horizontal plane. However, in ten cases, the efferent and afferent limbs crossed or touched each other; this occurred in the middle third of the body in two, and in the distal third in eight cases. The portion of the loop distal to the crossing was always very narrow. In one case both limbs were completely super-

imposed, and were entirely anterior to zero; a terminal appendage, which was oriented slightly posteriorly, was present. Varying portions of the proximal part of the efferent limb of the body was anterior to the zero point in all the tracings; in some, posterior displacement occurred very early. Nonetheless, posterior displacement was never abrupt. The afferent limb, at least in part, was posterior in all but six instances. However, in these exceptional cases, anterior displacement of the end of the body never exceeded that of the initial forces (Fig. 4), and was always associated with a rightward appendage.

TABLE II. HORIZONTAL PLANE. MEASUREMENTS OF THE LONG AXIS (ANGLE) (SEE GRAPH I AND FIG. 1)

	MEAN	STANDARD DEVIATION	LARGEST POSITIVE	LARGEST NEGATIVE
Duchosal	+5.87	±4.57	+18.00	−8.00
Cube	+3.30	±5.74	+14.00	−19.00

TABLE III. HORIZONTAL PLANE. MEASUREMENTS OF INITIAL FORCES IN MILLIVOLTS (SEE FIG. 1)

	MEAN	MEDIAN	STANDARD DEVIATION	LARGEST OBSERVATION
Right	0.06	0.06	±0.04	0.26
Anterior	0.05	0.05	±0.03	0.16
Number of time interruptions	5.30 (0.012 sec.)	5.03 (0.012 sec.)	±1.94 (0.0049 sec.)	10.00 (0.025 sec.)

Each timing interruption equals 0.0025 second. There were no rightward initial forces in five subjects.

Measurements relevent to the body are given in Table IV. The widest part of the body was usually located in the proximal third, corresponding to the posterior bulge near its end. It should be noted that the widest part of the body did not necessarily coincide with that portion of the loop where the largest anterior and/or posterior vectors were situated (Fig. 1). Generally, if the long axis was anteriorly displaced, the most anterior portion of the body occurred in its distal third, and the most posterior in the proximal third; when the long axis was posteriorly displaced, the most anterior portion of the body tended to be in its proximal third and the most posterior portion in the distal third. Normal vectorial forces in the horizontal plane describe a smooth projection without sudden outpocketings, abrupt indentations, or square corners.

Terminal Appendage.—A rightward terminal appendage occurred in fifty-five cases, and varied from a linear to a hemioval projection. In a few of these the centripetal limb of the appendage deviated slightly to the left before returning to the null point. The terminal appendage was entirely posterior in all but six instances. In the latter the body of the loop was entirely anterior, consequently the terminal appendage was also anterior at its beginning; however, it ultimately

TABLE IV. HORIZONTAL PLANE. MEASUREMENTS OF BODY IN MILLIVOLTS (SEE FIG. 1). ALSO RATIO OF VARIOUS MEASUREMENTS OF INITIAL FORCES AND APPENDAGE TO VARIOUS BODY MEASUREMENTS

	MEAN	MEDIAN	STANDARD DEVIATION	LARGEST OBSERVATION	SMALLEST OBSERVATION
Width (body)	0.15		±0.06	0.32	In one case both limbs of body were superimposed and associated with a rightward appendage
Anterior (body)	0.15	0.14	±0.08	0.37	0.03
Posterior (body)	0.09	0.08	±0.05	0.25	Body may be entirely anterior when associated with a rightward appendage
Leftward (body)	0.86		±0.25	1.65	0.20
Width (body) / Leftward (body)	0.19		±0.10	0.55	
Rightward (initial forces) / Leftward (body)	0.07		±0.04	0.21	Initial forces may be absent
Rightward (appendage) / Leftward (body)	0.17		±0.10	0.41	Appendage may be absent
Sum of rightward (initial forces) and leftward forces (of body). (Overall length of loop)	0.89		±0.30	1.84	0.21

became posteriorly oriented (Fig. 4). A summary of measurements pertaining to the terminal appendage is given in Table V. Large, terminal appendages, maximal duration of appendages, and slow inscription of the terminal forces were commonly associated.

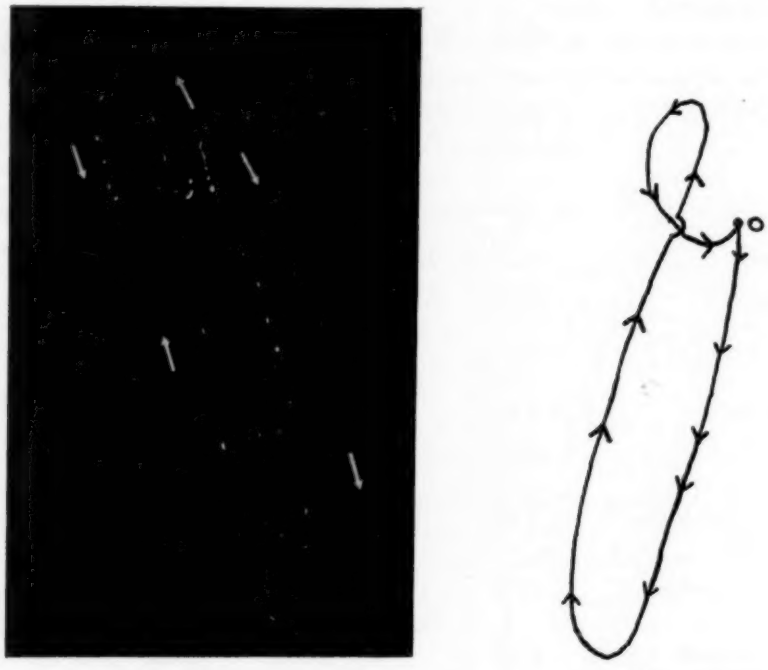
TABLE V. HORIZONTAL PLANE. MEASUREMENTS OF TERMINAL APPENDAGE IN MILLIVOLTS (SEE FIG. 1)

	MEAN	MEDIAN	STANDARD DEVIATION	LARGEST OBSERVATION
Right	0.12	0.10	±0.09	0.39
Posterior	0.09	0.08	±0.06	0.25
Number of time interruptions	8.80 (0.022 sec.)	8.38 (0.006 sec.)	±3.50 (0.0087 sec.)	18.00 (0.045 sec.)

Each timing interruption equals 0.0025 second. A terminal rightward appendage occurred in fifty-five subjects.

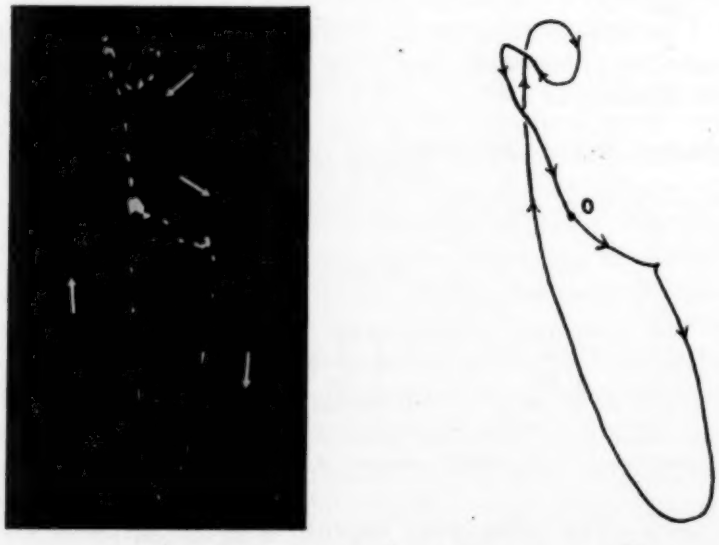
Sagittal Plane.—The loops were smooth, slightly flattened ovals with a variable amount of posterior bulging terminally; the maximum duration was 0.095 second (38 interruptions). The early and terminal vectors were slowly inscribed in most cases, the former up to 25 per cent, the latter as much as 40

per cent of the total duration of the QRS. In less than half the cases the distal portion of the body, where a change in direction of forces occurred, showed slow inscription. The initial forces and body of the loop in all, and the terminal ap-



A. *B.*

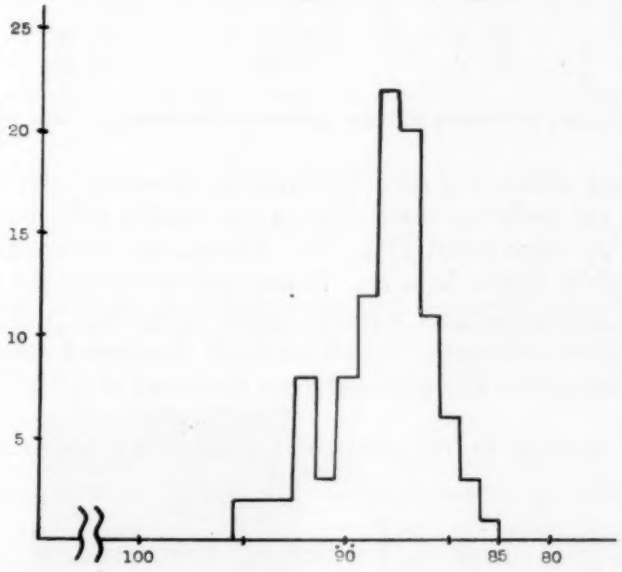
Fig. 5.—*A*, Sagittal plane. The QRS is clockwisely inscribed except for the terminal appendage, which is predominantly counterclockwise, and dips inferiorly before reaching zero. The earliest QRS forces go down and are slowly inscribed. (See *B*.) *B*, Diagram of *A*. QRS. The arrows indicate the sequence of inscription.



A. *B.*

Fig. 6.—*A*, Sagittal plane. QRS loop. The body is clockwisely inscribed and its terminal portion is barely posterior to zero. The terminal appendage is superimposed and is posterior to zero except for an anterior outpocketing which is clockwisely inscribed. (See *B*.) *B*, Diagram of *A*. QRS. Arrows indicate sequence of inscription.

pendage in most cases, were clockwisely inscribed. In some vectorcardiograms with superior and entirely posterior terminal appendages, the latter, even when presenting a figure-of-eight configuration, were usually inscribed in a clockwise direction. The distal portion of the appendage in these was very narrow. In one case in which the terminal appendage was entirely posterior, an abrupt change to counterclockwise inscription occurred and persisted to the end of the QRS, and the terminal vectors dipped somewhat inferiorly before reaching the null point (Fig. 5). This loop did not have a terminal rightward component in the horizontal and frontal planes. In two tracings, in which the initial forces and body of the loop were entirely anterior, the beginning of the terminal appendages was also slightly anterior, and was counterclockwisely inscribed throughout.



Graph II.—The QRS long axis (angle) in the sagittal plane of 100 normal patients, obtained by the Duchosal method. An angle greater than 90° indicates posterior displacement, less than 90°, anterior displacement. Ordinates represent number of individuals, abcissae, the long axes in degrees.

A terminal rightward component was present in these two cases in the horizontal and frontal planes. In a fourth case, in which the late portion of the body was slightly posterior, the terminal appendage was also posterior, except for an anterior outpocketing (notch) near its beginning; the outpocketing was clockwisely inscribed (Fig. 6).

The long axis is defined as the angle subtended by a horizontal line drawn through the zero point and the maximal vector. The angle is 90 degrees when the maximal vector is prependicular to the horizontal line, less than 90 degrees when anteriorly displaced, and greater than 90 degrees when posteriorly displaced. The angles varied between 97 and 85 degrees with the Duchosal reference system compared to 102 and 80 degrees with the Cube system (Table VI). It was not invariably greater with one system than with the other. The angles for the 100 cases are plotted in Graph II.

Initial Forces.—Sixty-four subjects had initial forces. They had a hemioval configuration. The afferent and efferent limbs, except when very small, were never superimposed. In all instances the initial forces were entirely anterior. The efferent limb, particularly when the long axis in the frontal plane was vertical, usually went straight up from the zero point with but little anterior deviation. This finding is contrary to that of others.[14] The afferent limb, however, had a more anterior orientation. Table VII summarizes the data pertaining to initial forces.

TABLE VI. SAGITTAL PLANE. MEASUREMENTS OF THE LONG AXES (ANGLE)

	MEAN	STANDARD DEVIATION	LARGEST OBSERVATION	SMALLEST OBSERVATION
Duchosal	89.72	±2.45	97.00	85.00
Cube	89.31	±4.55	102.00	80.00

An angle greater than 90 degrees indicates posterior displacement. (See Graph II and Fig. 2.)

In three cases with initial superior forces the proximal part of the descending efferent limb of the body reversed its direction temporarily, but in so doing did not rise above the zero point (Fig. 7). Among the three cases the maximal voltage of the initial forces (*a* in Fig. 7) was 0.01 millivolt, the maximal voltage measured from zero when this reversal began (*b* in Fig. 7) was 0.03 millivolt. The point at which the trace started its final downward course (*c* in Fig. 7) never occurred later than 0.025 second after the onset of QRS.

TABLE VII. SAGITTAL PLANE. MEASUREMENTS OF INITIAL FORCES IN MILLIVOLTS (SEE FIG. 2)

	MEAN	MEDIAN	STANDARD DEVIATION	LARGEST OBSERVATION
Superior	0.08	0.08	±0.07	0.37
Anterior	0.05	0.05	±0.03	0.16
Number of time interruptions	5.16 (0.013 sec.)	4.73 (0.011 sec.)	±2.0 (0.005 sec.)	10.0 (0.025 sec.)

Each timing interruption equals 0.0025 second. There were no superior initial forces in thirty-six subjects.

Initial forces were absent in thirty-six cases. In these the earliest vectors were oriented inferiorly and anteriorly. In seven the inferior course of the earliest part of the loop was interrupted by a temporary reversal to a superior orientation, though without passing above the null point (Fig. 8). Among the seven cases the largest vector prior to reversal of direction was 0.25 millivolt, and the longest interval from the zero point to the instant when the loop began its second inferior course was 0.025 second.

Body of the Loop.—As already stated, the body of the loop had a hemioval configuration in the sagittal plane, although the afferent and efferent limbs touched or crossed each other in nine cases. In seven instances this occurred in

the distal third, and in two in the middle third of the body. The portion of the body distal to the crossing was very narrow. The body was inscribed in a clockwise direction without exception, though in one case the afferent and efferent limbs were superimposed. The proximal part of the efferent limb was always anterior. Posterior deviation, which began very early in some, was never abrupt.

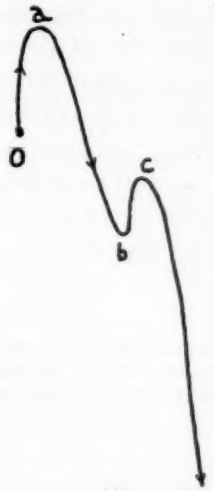
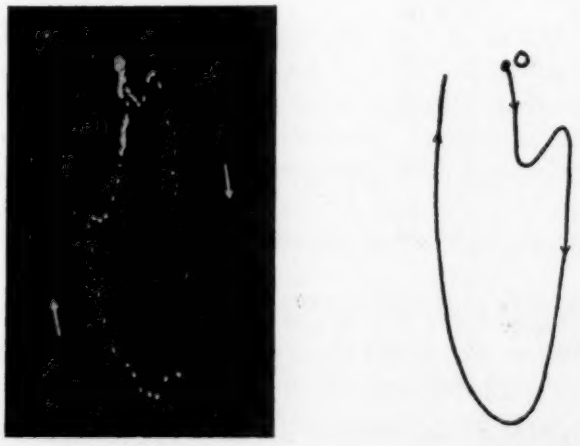


Fig. 7.—Diagram of earliest QRS vectors in the sagittal plane in three cases described in text. Following the superior initial forces the proximal part of the descending efferent limb of the body reversed its direction temporarily, but in so doing did not rise above the zero point. Arrows indicate sequence of inscription.



A. *B.*

Fig. 8.—*A*, Sagittal plane. QRS. Earliest vectors are oriented inferiorly with increasing magnitudes except at the beginning of the loop (see text). The terminal part of the loop as well as the earliest vectors and distal part of the body are slowly inscribed. (See *B*.) *B*, Diagram of *A*. QRS. Arrows indicate sequence of inscription.

The afferent limb was posterior at least in part, except in two instances. In these the entire sagittal projection of the initial forces and body was anterior. These two cases were associated with a terminal superior and rightward appendage which, at least in its latter portion, was posterior to zero.

It should be noted that the initial forces and body were entirely anterior to zero in the horizontal projection in six vectorcardiograms compared to two in the sagittal plane. This discrepancy is due to the fact that part of the final portion of the rightward appendage is posterior and inferior; therefore it appears as part of the body in the sagittal plane and as part of the terminal appendage in the horizontal plane.

The widest part of the body did not necessarily comprise that portion where the forces were maximally anterior and/or posterior (Fig. 2). As a rule, if the long axis in the sagittal plane was less than 90 degrees, the most anterior portion of the body occurred in the distal third. If the long axis exceeded 90 degrees, the most anterior part of the body was in the proximal third. This follows because the sagittal projection usually described a smooth curve without gross outpocketings or indentations, though in a few instances slightly irregular projections occurred. Table VIII summarizes the above data pertaining to the body in the sagittal plane.

TABLE VIII. SAGITTAL PLANE. MEASUREMENTS OF BODY IN MILLIVOLTS (SEE FIG. 2). ALSO RATIO OF VARIOUS MEASUREMENTS OF INITIAL FORCES AND APPENDAGE TO VARIOUS BODY MEASUREMENTS

	MEAN	MEDIAN	STANDARD DEVIATION	LARGEST OBSERVATION	SMALLEST OBSERVATION
Width (body)	0.15		±0.06	0.32	0.03
Anterior (body)	0.10		±0.05	0.26	0.02
Posterior (body)	0.09		±0.05	0.32	Body may be entirely anterior
Inferior (body)	1.50		±0.53	3.03	0.32
Width (body) / Inferior (body)	0.11		±0.08	0.54	0.02
Superior (initial forces) / Inferior (body)	0.05		±0.04	0.17	Initial forces may be absent
Superior (appendage) / Inferior (body)	0.20		±0.16	0.72	Terminal appendage may be absent
Sum of initial superior forces and inferior forces of body (overall length of loop)	1.52	1.49	±0.58	3.11	0.32

Terminal Appendage.—A terminal superior appendage occurred in fifty-two cases. The ratio of the maximal superior vector of the appendage to the maximal inferior vector of the body was related to the long axis of the QRS loop in the frontal plane, and will be discussed later (Table XIV). As previously mentioned, the last vectors of the terminal appendage in a few cases were slightly inferior before returning to zero. There were two instances in which the terminal appendage had a superior magnitude of 0.14 and 0.06 millivolt, respectively, and an almost equal voltage in the opposite direction before returing to zero (Fig. 5).

The terminal appendage varied in shape from a linear projection to hemioval. Large terminal vectors, maximal duration of the appendage, and slow inscription

of terminal forces were frequently coexistent. Table IX summarizes the characteristics of the terminal appendage in the sagittal plane.

Frontal Plane.—The loops in this projection displayed the greatest variability. A flattened oval or ellipse occurred in most, and a relatively circular loop or figure-of-eight configuration in the rest. Gross sudden changes in direction rarely occurred. Others have observed similar findings using the Tetrahedron reference system.[2] Maximum duration of the QRS loop was 0.095 second (38 interruptions). The early and terminal forces were usually slowly inscribed, the former up to 25 per cent, the latter as much as 40 per cent of the total duration of QRS. The distal portion of the body, where a change in direction of forces occurred, often showed slow inscription.

TABLE IX. SAGITTAL PLANE. MEASUREMENTS OF TERMINAL APPENDAGE IN MILLIVOLTS (SEE FIG. 2)

	MEAN	MEDIAN	STANDARD DEVIATION	LARGEST OBSERVATION
Posterior	0.09	0.08	±0.04	0.26
Superior	0.23	0.21	±0.14	0.53
Number of time interruptions	10.5 (0.026 sec.)	9.85 (0.0248 sec.)	±3.40 (0.0087 sec.)	18.0 (0.045 sec.)

Each timing interruption equals 0.0025 second. A terminal superior appendage occurred in fifty-two cases.

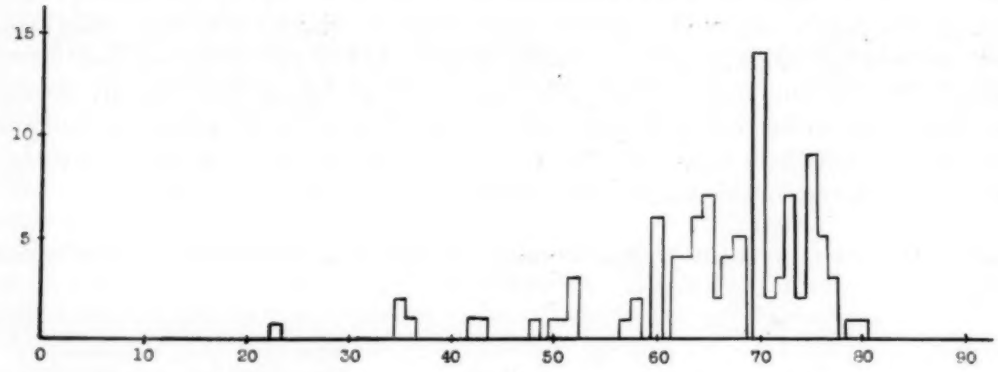
The long axis is defined by the angle alpha (α) which is the angle subtented by the maximal vector and the horizontal line drawn through the zero point. Angle α is 0 degrees when the maximal vector coincides with, and is 90 degrees when perpendicular to the horizontal line (Fig. 3). The angles varied between + 23 and + 80 degrees with the Duchosal reference system, compared to + 16 and + 70 degrees with the Cube system (Table X), and was invariably greater with the Duchosal than with the Cube system. The angles for the 100 cases are shown in Graph III.

Initial Forces.—The initial forces went to the right in all but three cases, in which they were oriented inferiorly and to the left in two, and slightly superiorly and to the left in one; in these angle α was 75, 65, and 63 degrees, respectively. The body was clockwisely inscribed in the frontal plane in all three instances.

TABLE X. FRONTAL PLANE. MEASUREMENTS OF THE LONG AXES (ANGLE α) (SEE GRAPH III AND FIG. 2)

	MEAN	STANDARD DEVIATION	LARGEST OBSERVATION	SMALLEST OBSERVATION
Duchosal	65.69	±10.49	80.00	23.00
Cube	40.41	±16.01	70.00	16.00

The trace of initial forces varied from that of a hemioval to a linear projection or figure of eight. The initial forces were often inscribed in a direction opposite to that of the body. Table XI summarizes the data relevant to initial forces.



Graph III.—The QRS long axis (angle α) in the frontal plane of 100 normal patients, obtained by the Duchosal method. Ordinates represent number of individuals, abcissae, the long axes in degrees.

The initial forces were oriented superiorly and to the right in sixty-seven cases. In many the initial forces assumed an inferior direction before crossing to the left of zero. In three of these the latter inferior portion of the initial forces displayed a temporary reversal in direction, but in so doing did not rise above the zero point (Fig. 9). The maximal voltage, in the three cases, of the superior initial forces (*a* in Fig. 9) was 0.01 millivolt, the maximal voltage measured when reversal began (*b* in Fig. 9) was 0.03 millivolt. The point at which the trace started its final downward course (*c* in Fig. 9) never occurred later than 0.025 second after the onset of the QRS.

TABLE XI. FRONTAL PLANE. MEASUREMENTS OF INITIAL FORCES IN MILLIVOLTS (SEE FIG. 3)

	MEAN	MEDIAN	STANDARD DEVIATION	LARGEST OBSERVATION
Superior	0.08	0.07	±0.08	0.40
Right	0.06	0.05	±0.05	0.28
Number of time interruptions	6.31 (0.016 sec.)	6.50 (0.016 sec.)	±2.00 (0.005 sec.)	11.0 (0.0275 sec.)

Each timing interruption equals 0.0025 second.

There was a correlation between the angle subtended by the initial forces and the horizontal line, and the long axis. As the long axis became more perpendicular the initial forces tended more and more to go straight up or straight down. However, there were five instances in which relatively perpendicular loops had initial forces which went straight out before going up or down.

There was a correlation between the duration of that part of initial forces superior to zero, and the long axis. The longest duration was 0.015 second when the angle was + 55 degrees, 0.0075 second for an angle of + 48 degrees, and 0.005 second for angle α of + 35 degrees. The longest duration was 0.0275 when the angle exceeded + 55 degrees. Initial superior forces were consistently absent when the angle was + 35 degrees or less.

The maximal voltage of the initial superior forces was 0.394 millivolt, when the angle of the long axis was + 65 degrees or more, and 0.105 millivolt when the angle was less than + 65 degrees.

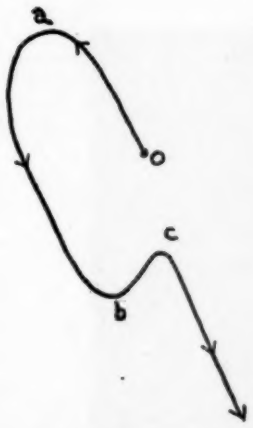


Fig. 9.—Diagram of earliest QRS vectors in the frontal plane in three cases described in text. Following the right and superior initial forces, the inferior portion of initial rightward forces reversed its direction temporarily, but in so doing did not rise above the zero point. Arrows indicate sequence of inscription.

There were twenty-three instances in which the initial rightward forces went down without interruption, and the long axes in these varied from + 76 to + 25 degrees (Table XII). These initial forces were counterclockwisely inscribed without exception.

TABLE XII. FRONTAL PLANE. THE NUMBER OF SUBJECTS, ACCORDING TO THE LONG AXIS, WHOSE INITIAL RIGHTWARD FORCES WENT EXCLUSIVELY INFERIOR WITHOUT INTERRUPTION (SEE TEXT)

Long axis	70–80	60–69	50–59	23–49
Number	13	6	2	2

In addition to the twenty-three cases there were seven in which the inferior course of the initial rightward forces was interrupted by a temporary reversal in direction to a superior orientation, though without passing above the null point (Fig. 10). Among the seven cases the largest inferior vector prior to reversal was 0.25 millivolt, and at the second point of reversal, 0.07 millivolt. The longest interval from the zero point to the instant when the loop began its second inferior course was 0.025 second. The long axes in these seven cases were

+ 72, + 68, + 67, + 65, + 52, + 43, and + 35 degrees. In all seven instances the initial forces were either counterclockwisely inscribed or a crossover was present (Fig. 10). Clockwise inscription did not occur in these.

Body of the Loop.—The body of the frontal loop, as noted above, varied greatly in shape. Sudden changes of direction rarely occurred, and the contour remained smooth in spite of many crossings.

The greatest width of the body was observed in vertical loops which were clockwisely inscribed and horizontal loops which were counterclockwisely inscribed (Table XIII). This relationship between angle α and direction of inscription was the rule.

A. *B.*

Fig. 10.—*A*, Frontal plane. QRS. The initial forces, counterclockwisely inscribed, are oriented to the right and inferiorly with increasing magnitude, though interrupted by a temporary reversal to a superior orientation without going above the zero point. (See text.) This vectorcardiogram was taken to show the initial forces without superimposed P and T loops. Therefore, it appears to be incomplete. *B*, Diagram of *A*. The beginning of the QRS loop in frontal plane. Arrows indicate sequence of inscription.

However, thirteen cases with an angle α of 70 degrees or more were entirely, or for the most part, counterclockwisely inscribed, but these were usually narrow, the greatest width measuring 0.28 millivolt. There were sixteen cases in which angle α fell between 60 and 69, and in which the loops were counterclockwisely inscribed; the greatest width in this group was 0.46 millivolt.

Clockwisely inscribed loops with an angle α of 40 degrees or less occurred in three cases; they were very narrow or figure of eight in configuration in two instances. However, in spite of an angle of 36 degrees in one case, the body had a relatively circular configuration and measured 0.59 millivolt in width.

The most horizontal loop in this series had an angle α of 23 degrees, and was very narrow and displayed many crossings. The most perpendicular loop in this series had an angle α of 80 degrees, was clockwisely inscribed, and had a width of 0.50 millivolt (relatively circular).

Width of the body is defined as the widest part of the body and is measured to the left of zero and parallel to the horizontal line (Fig. 3). Table XIII summarizes the measurements of the body.

Terminal Appendage.—Terminal appendages occurred in seventy-two vectorcardiograms: These were oriented to the right and superiorly in forty, to the right and inferiorly in thirteen, and to the left and superiorly in nineteen.

The body was clockwisely inscribed in all instances in which the terminal appendage was directed to the right and entirely inferiorly, and the appendage in these cases was always inscribed in the same direction. Figure-of-eight configuration of the appendage was not noted in any of these. In the other two groups the appendages and bodies were variously inscribed. However, if a crossing occurred in an appendage, the portion of the appendage distal to the crossing was very narrow.

TABLE XIII. FRONTAL PLANE. MEASUREMENTS OF BODY IN MILLIVOLTS (SEE FIG. 3). ALSO RATIO OF VARIOUS MEASUREMENTS OF INITIAL FORCES AND APPENDAGE TO VARIOUS BODY MEASUREMENTS

	MEAN	MEDIAN	STANDARD DEVIATION	LARGEST OBSERVATION	SMALLEST OBSERVATION
Width (body)	0.24		±0.13	0.60	0.05
Inferior (body)	1.52	1.43	±0.35	3.02	0.30
Left (body)	0.78	0.78	±0.26	1.63	0.21
Length (body)	1.67	1.67	±0.52	3.16	0.63
Length (initial forces) / Length (body)	0.07		±0.33	0.17	Initial forces may be absent
Sum of length of initial forces and length of body	1.75		±0.58	3.63	0.63
Width (body) / Length (body)	0.16	0.13	±0.12	0.68	0.03
Superior (appendage) / Inferior (body)	0.20		±0.15	0.71	Appendage may be absent

There were two instances in which the terminal, superior, and rightward appendages had superior magnitudes of 0.14 and 0.06 millivolt, respectively, and almost equally large vectors oriented to the right and inferiorly at the very end of the loop.

TABLE XIV. FRONTAL PLANE. RATIO OF THE SUPERIOR DEVIATION OF THE TERMINAL APPENDAGE TO THE INFERIOR DEVIATION OF THE BODY

Long axis	70–80	60–69	50–59	23–49
Maximal ratio of Superior deviation (appendage) / Inferior deviation (body)	0.30	0.38	0.59	0.72

The results are grouped according to angle α (long axis) in the frontal plane.

There was one case in which a superior leftward appendage had a superior magnitude of 0.10 millivolt and an almost equal voltage to the left and inferiorly before returning to zero.

The ratio of the length of the appendage to the length of the body is given in Table XIV. This ratio varies in accordance with angle α; the superior forces of the appendage tended to be greater, and the inferior forces of the body smaller, in the more horizontal loops.

There was an association of large appendages, maximal duration of these appendages, and slowness of inscription of these forces. Table XV summarizes the data in relation to the appendage.

TABLE XV. FRONTAL PLANE. MEASUREMENTS IN MILLIVOLTS OF TERMINAL APPENDAGE (SEE FIG. 3)

	MEAN	MEDIAN	STANDARD DEVIATION	LARGEST OBSERVATION
Superior	0.23	0.21	±0.13	0.53
Rightward	0.12	0.10	±0.96	0.40
Maximal vector	0.26		±0.12	0.58
Width	0.17		±0.10	0.57
Number of time interruptions	10.84 (0.027 sec.)	8.50 (0.021 sec.)	±3.20 (0.008 sec.)	18 (0.045 sec.)

Each timing interruption equals 0.0025 second.

T Loop and S-T Junction.—The actual length of the maximal T vector and the angle between the long axis of the QRS and the T loop is summarized in Table XVI. This angle is positive if the T is anterior or to the right of the QRS long axis, and negative if the relations are reversed. In most cases the T axis was slightly anterior to the QRS, but in some both axes were superimposed and in a few the long axis of T was slightly posterior to the QRS. These results were similar to those of others.[3,9] When the long axes of QRS and T were both posterior to zero, the latter was still anterior to the former. The T long axis in the frontal plane was more often to the right (positive) than to the left (negative) of the QRS long axis (Table XVI).

TABLE XVI. MEASUREMENTS IN MILLIVOLTS OF MAXIMAL VECTOR OF T LOOP. THE DIFFERENCE (ANGLE) BETWEEN THE LONG AXIS OF THE QRS AND T LOOP

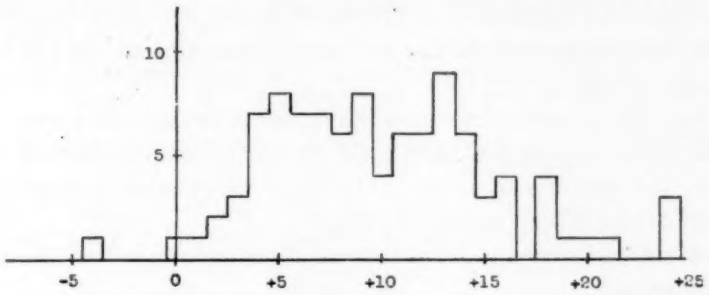
		MEAN	STANDARD DEVIATION	LARGEST OBSERVATION	SMALLEST OBSERVATION
Horizontal	T loop length	0.27	±0.08	0.46	0.08
	Difference between long axis of T and QRS	+4.06	±3.83	+18.0	−5.0
Sagittal	T loop length	0.47	±0.17	1.05	0.11
	Difference between long axis of T and QRS	+2.61	±1.95	+10.0	−4.0
Frontal	T loop length	0.49	±0.16	1.05	0.21
	Difference between long axis of T and QRS	+3.34	±6.76	+30.0	−10.0

A positive value indicates the T axis is anterior or to the right (frontal plane) of QRS.

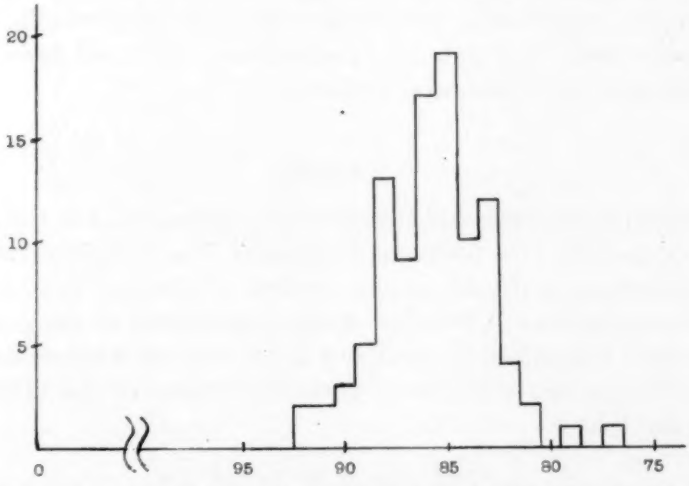
Graphs IV, V and VI show the data relevant to the long axis of the T loop in the three planes. T loops were usually three times greater in length than width

and are similar to the observations reported by others with the Tetrahedron reference system.[2]

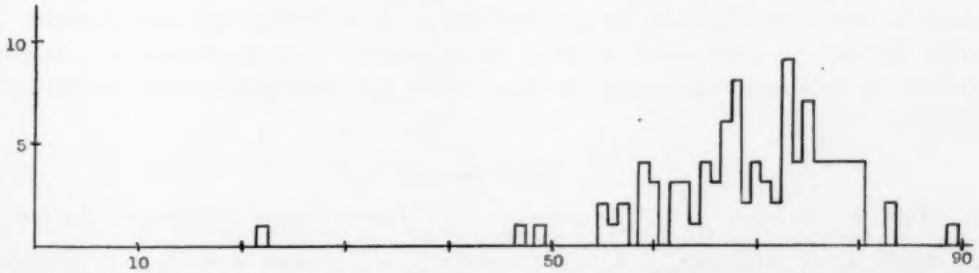
The direction of inscription of the T loop was ascertained in seventy-five cases. The direction in the horizontal and sagittal plane was always the same as that of the QRS. In the frontal plane, though usually similar, opposite inscription occurred in some cases when the QRS was very narrow.



Graph IV.—The T long axis (angle) in the horizontal plane of 100 normal patients, obtained by the Duchosal method. Ordinates equal number of individuals, abcissae, the long axes in degrees.



Graph V.—The T long axis (angle) in the sagittal plane of 100 normal patients, obtained by the Duchosal method. An angle greater than 90° indicates posterior displacement, less than 90°, anterior displacement. Ordinates represent number of individuals, abcissae, the long axes in degrees.



Graph VI.—The T long axis (angle α) in the frontal plane of 100 normal patients, obtained by the Duchosal method. Ordinates represent number of individuals, abcissae, the long axes in degrees.

The S-T junction was usually located at the null point (closed loops). In six cases the S-T junction (J) was slightly deviated to the left and inferiorly, and in three instances to the right and superiorly.

DISCUSSION

The above data have been obtained primarily to serve as the standard for the normal vectorcardiogram and to indicate a method of analysis.

The many variations that are observed in normal and abnormal vectorcardiograms pose difficulties that must be overcome before vectorcardiography can be useful as a diagnostic tool. These variations include the general morphology, position, and magnitude of QRS and T vectors, their direction and speed of inscription, the interrelationships of various portions of the QRS loop, and of the latter to the T loop.

All of the above considerations have been detailed in this study of the normal. Special attention has been paid to variations in position and direction of inscription, the relation of these factors not only to each other, but to many other features of the entire spatial figure.

Morphologic variations (contour) are difficult to measure and are, therefore, qualitatively defined.

The results by the method of analysis used in this series of normal subjects have been tested against the vectorcardiograms as found in right and left ventricular hypertrophy, myocardial infarction, right and left bundle branch block, intraventricular block, and pulmonary embolism, and have been found to constitute a valid basis for differential diagnosis.

SUMMARY

The horizontal, sagittal, and frontal planar projections of the spatial vectorcardiogram are described for 100 normal subjects. The Trihedron reference system was used. Emphasis is placed upon a method of analysis that may be applied to any reference system. A detailed study is presented of the general morphology, position, and magnitude of QRS and T vectors, their direction and speed of inscription, the interrelationships of various portions of the QRS loop, and of the latter to the T loop.

SUMMARIO IN INTERLINGUA

Un detaliate analyse quantitative esseva facite del vectocardiogrammas de 100 individuos in bon stato de sanitate con cordes normal. Le methodo usate in iste investigation es applicabile a vectocardiogrammas obtenite per medio de non importa qual quadro de referentia. Le resultatos se concentra intra nette limites e representa un base valide pro interpretationes vectorcardiographic.

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PERFORATION OF THE INTERVENTRICULAR SEPTUM COMPLICATING MYOCARDIAL INFARCTION

A Report of Eight Cases, One With Cardiac Catheterization

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PERFORATION of the interventricular septum is one of the more uncommon complications following acute myocardial infarction. A review of the literature, however, reveals that this complication, during recent years, has been recognized more frequently. Latham[1] first described the pathology of this complication in 1845 and outlined the criteria for its clinical recognition. The first ante-mortem diagnosis was made by Brunn,[2] seventy-eight years after the pathologic description was first published. The first comprehensive study of the condition by Sager,[3] in 1934, revealed the world literature to then consist of eighteen cases. During the next twenty years, seventy-five additional cases were reported, so that when Bond[4] reviewed the literature in 1953, there were ninety-three cases. There have been thirty-one more case reports published during the past two years, and with the eight cases to be presented here, the number of reported cases of septal perforation now totals one hundred and thirty-two.

The clinical diagnosis of septal perforation following myocardial infarction was a relatively unknown occurrence prior to the year 1942. Of the first thirty-five cases reported in the literature, only five were diagnosed before death.[5] However, there has been an increasing awareness of this complication, and recent reports have revealed that the majority of cases have been suspected prior to death. Thus, all of Bond's five cases[4] and three of Nareff's four cases[6] were diagnosed ante mortem.

Perforations of the ventricular septum may be missed at post-mortem examination because of the coarse trabeculation of the lower portion of the septum, and because many of these perforations are small and covered by thrombi.

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Therefore, it is important for the clinician to alert the prosector of the possibility of a septal perforation. To illustrate how easily these perforations may escape detection, one of our cases may be cited. In this instance, the diagnosis was not made ante mortem, nor was the defect originally detected at autopsy. However, later, another interested observer re-examined the heart and found a small perforation. When the patient's chart was reviewed, it was discovered that a loud precordial systolic murmur had appeared suddenly, a few hours before the patient expired; however, this had not been mentioned in the original summary. Had the diagnosis of a septal perforation been considered prior to death, and the prosector alerted to the possibility, the defect could have been demonstrated by pouring water into the unopened left ventricle and by careful inspection of the septum.

Evaluation of our eight cases discloses that only three were diagnosed ante mortem. Of the remaining five, one was just described; in two others, loud murmurs were present on admission, but the patients expired within a few hours; and in the other two patients, there was a rupture of both the septum and the free ventricular wall. Both of these patients expired suddenly, before anyone had an opportunity to observe a murmur.

It is the purpose of this paper to present eight new cases of septal perforation, and to review the literature on this subject. Six of these cases were seen within a ten-month period. Seven of the cases were confirmed at post-mortem examination, and the eighth case is still living. This one surviving patient is of particular interest because confirmatory evidence of the septal perforation was sought for by cardiac catheterization. The only other reported use of catheterization in this condition was from Norway, by Muller[7] in 1950. Two other cases presented the unusual combination of a ruptured heart, together with a septal perforation.

Pertinent information relative to these patients is summarized in Table I. The complete case reports have been omitted at the suggestion of the editor in the interest of decreasing the volume of the text.

DISCUSSION

Clinical Picture.—When there is sufficient time to observe a patient and the possibility of this complication is considered, the diagnosis of a ruptured septum is not difficult. It is marked by the appearance of a loud, low-pitched, blowing systolic murmur at the left sternal border in the fourth or fifth intercostal spaces and transmitted towards the apex. It is frequently accompanied by a systolic thrill in the same location. Although the pulse is feeble and the heart tones distant, the murmur is usually loud and distinct, and in only two cases has no murmur been described. One patient[8] was in coma, had no obtainable blood pressure, and died shortly after admission. Autopsy revealed a large septal defect. The other patient[9] was observed over a five-day period, during which an adequate blood pressure was maintained. Post-mortem examination again revealed a large 2 cm. by 0.5 cm. septal defect. No good explanation could be offered for the absence of a murmur.

TABLE I. EIGHT CASES OF INTERVENTRICULAR SEPTAL PERFORATION

CASE	AGE	SEX	DAY MURMUR NOTED	DEATH AFTER PERFORATION	ELECTROCARDIOGRAM	PATHOLOGY	SIZE OF PERFORATION
W.M.	70	M	3rd day	19 days	QSV_1-V_6; elev. S-TV_1-V_6; borderline $Q_{II,III}$, and aV_F	Thromboses, left descending coronary; recent anteroseptal and old posterior infarcts	1.5 cm.
E.V.	69	M	5th day	Few hours	QS and elev. S-TV_{2R}-V_5	Thromboses, left coronary; recent anteroseptal infarction	2 mm.
D.G.	68	M	5th day	Living now 9 months	QSV_1-V_4; elev. S-$T_{I,II}$, and V_1-V_6; $T_{I,II}$, aV_L	Still living	
L.W.	62	M	1st day	5 hours	QS and elev. S-$T_{II,III}$, aV_F, V_5-V_6	Thromboses, left circumflex coronary, posterolateral infarction	2 mm.
C.H.	72	F	On admission	1 day	None	Occlusion, right coronary; acute anterior and posterior infarctions	2 cm.
J.D.	74	M	On admission	1 day	QR, elev. S-T, and TaV_R, V_2-V_6	Thromboses, left descending coronary; acute anterolateral infarction	4 cm.
C.T.	72	F	No murmur	Few hours	QSV_3-V_5; elev. S-T_I, aV_L, and V_2-V_6	Thromboses, left descending coronary; acute anterolateral infarction with 1 cm. rupture of left ventricle	2.5 cm.
M.H.	76	F	No murmur	Two hours	QS, elev. S-$T_{II,III}$ and aV_F	Thromboses, right descending coronary; acute postseptal infarction with 3 mm. rupture of right ventricle	3.5 cm.

A diastolic murmur has been described in only four cases, each associated with an enlarged dilated heart, which may be the explanation for the murmur. There have been other explanations for the murmur, however, including a large perforation,[3] or the presence of a concomitant ventricular aneurysm.[10]

The systolic murmur usually appears within the first seven days following infarction. In the cases reported here, four appeared on the first day, one on the third day, and two on the fifth day. A few cases have ruptured later than the seventh day, but none after one month.

The development of a perforation is usually associated with a sudden change in the clinical course. Edmondson and Hoxie[11] pointed out that, in their cases, there was an average fall in the systolic blood pressure of 75 mm. Hg (from 160/100 mm. Hg to 85/60 mm. Hg). There is often a sudden recurrence or intensification of chest pain, with the development of shock or congestive failure, which initiates a fairly rapid downhill course.

Electrocardiogram.—There have been several reports in the recent literature dealing with the electrocardiographic patterns in septal infarction. Wilson[12] and his collaborators first pointed out, in 1946, the association of septal infarction with electrocardiographic evidence of both anterior and posterior myocardial infarction. One year later, Roesler and Dressler[13] presented five cases of septal infarction confirmed at autopsy. The electrocardiograms in these cases showed a Q_3-T_3 pattern, suggesting posterior infarction, together with changes in the right precordial leads indicative of anterior infarction. They concluded that when this electrocardiographic pattern occurs, an extensive septal infarction should be strongly considered. However, Osher and Wolff[14] later pointed out that, although this pattern is characteristic of a septal infarction, it is seen infrequently. In twenty-five cases of concomitant infarction of both anterior and posterior walls, they found only two cases with this electrocardiographic pattern, and five others with suggestive changes.

Myers,[15] in a comprehensive study of the electrocardiographic findings in septal infarctions, found diagnostic evidence of septal damage in 68 per cent of anterior infarcts and 33 per cent of posterior infarcts. According to Myers, the following diagnostic features were found in septal infarction: a qrS configuration in the right precordial leads without evidence of right ventricular hypertrophy; a QS configuration in right precordial leads with either S-T segment changes in those leads, or normal R waves further to the right, or abnormal Q waves further to the left; and a Q_3-T_3 pattern with right precordial changes typical of infarction.

Employing his criteria in thirty-one cases of septal perforation (taken from the literature), where complete electrocardiograms were available, the significant features are outlined in Table II.

QS or qrS configurations were the commonest findings, present in 35 per cent of the cases. These supposedly represent a transmission of the left ventricular cavity potential through the infarcted septum. Right bundle branch block was the commonest conduction defect seen, present in 26 per cent of the cases. There were only four cases, 13 per cent, in which there was no electrocardiographic

TABLE II. ECG FINDINGS IN 31 CASES OF SEPTAL INFARCTION WITH PERFORATION

	CASES	PER CENT
1. Conduction defects	12	39
Right bundle branch block 8		
A-V block 4		
2. qrS or QS over right precordium with elevated S-T segments	11	35
3. Q_3R_3 with diagnostic features of anterior infarction	4	13
4. Posterior infarction without evidence of septal damage	4	13
Total	31	100

evidence of septal infarction. All four of these cases were posterior infarcts in which one commonly finds little or no electrocardiographic evidence of septal involvement.

Clinical Course and Prognosis.—The prognosis of a patient with a ruptured septum is very poor (See Table III).

TABLE III. SURVIVAL TIME FOLLOWING PERFORATION IN 91 CASES

	CASES	PER CENT
Less than 1 week	49	54
1 week to 2 months	30	33
2 months to 1 year	5	5.5
1 to 4 years	4	4.5
4 years to 5 years	2	2
6½ years	1	1
Total	91	100

Over 50 per cent of the patients die within the first week, and very few (13 per cent) survive the second month. The high mortality is probably due, in most cases, to the fact that the complication of septal perforation usually is indicative of extensive infarction. The perforations are usually not large enough, in themselves, to alter significantly the hemodynamic state. However, in those patients with a borderline cardiac reserve, the additional work load to the heart superimposed by the perforation may be sufficient to precipitate acute cardiac failure.

Those patients who survive the initial attack usually reveal evidence of congestive failure, which is refractory to treatment. There are, however, some exceptions: twelve patients have lived beyond two months, and seven beyond one year. Zucker[16] reported a patient who lived four and one-half years after his perforation. Woods and Livezey's[17] patient lived almost five years. Recently, Schlappi[18] has followed a patient for six and one-half years, who has the typical picture of a septal perforation, and was still living at the time of his report.

The course of these patients, when compared with the course of a patient with an uncomplicated myocardial infarction, reveals a striking difference.

Approximately 80 per cent of the patients having an uncomplicated myocardial infarction survive the initial attack, while 25 per cent are still living ten years after the initial episode.[19] These figures demonstrate the poor prognosis of a myocardial infarction that has been complicated by a septal perforation.

Pathology.—Infarction of the interventricular septum occurs in about 70 per cent of all cases of myocardial infarction.[14,15] Since the left coronary artery supplies the anterior two-thirds of the septum, it is not surprising to find that this portion of the septum is the most commonly infarcted, as the left coronary artery is thrombosed at least three times as often as the right. Thus, in a large series of infarcts, Hochrein[20] found the left coronary artery to be occluded in 74 per cent, the right coronary artery to be occluded in 21 per cent, and both vessels to be occluded in 8 per cent of the cases. The incidence of occlusion of these arteries in cases of septal perforation is approximately the same. The left coronary artery or its descending or circumflex branch was thrombosed, or otherwise occluded in 75 per cent, and the right coronary artery or its branches in 25 per cent of all the reviewed cases. The site of occlusion in our seven autopsied cases was the left coronary artery in five patients, and the right coronary artery in the remaining two patients. All occlusions were close to the origin of the vessel, and all were caused by thrombosis, except for patient C. H., in whom the vessel had been occluded by large atheromatous plaques.

Although rupture of the heart is the cause of death in from 8 per cent[21] to 9 per cent[22] of all deaths from acute myocardial infarction, and although the septum is involved in 70 per cent of all cases of infarction, perforation of the septum is uncommon. This is due, in part, to the good collateral circulation of the septum. But because infarction and necrosis of the septum are so common and often severe despite the good collateral, other factors may be important in predisposing to perforation.

The pathogenesis of septal perforation is the same as that of perforations of the heart in general. The most important factors are massive necrosis, lack of reparation, hypertension, and old age. Massive necrosis is unquestionably of main importance. The average time interval in our patients, between onset of pain and the time of perforation, was three and one-half days, with a range of from several hours to nine days. Histologically, this is the time that one finds the most extensive necrosis of the myocardium, the polymorphonuclear leukocytic infiltration is at its height, and the reparative processes have not yet begun.[23] These were the microscopic findings in all our cases, except that the necrosis was more severe than in the usual infarction. The next most important etiological factor is hypertension. The close relationship between rupture of the heart and increased intraventricular pressure has been pointed out by many authors.[11,22,24] The fact that hypertension is found more frequently among women may explain the finding that, although infarction is much more common among men, ruptures of the heart are relatively more common among women. The blood pressure was at shock levels in two of our patients, while among the remaining six, five had a systolic pressure of over 150 mm. Hg, and only one had a normal pressure. The youngest patient in our series was 62, the oldest 76.

There was no apparent correlation between perforation of the septum and cardiac hypertrophy. Six of the hearts examined weighed from 290 to 530 grams, and one weighed 870 grams.

Most septal perforations occur in the anteroapical portion of the septum, which is the area most frequently involved in all cases of septal infarction. The site of perforation was through the anterior portion of the septum in five of our patients and through the posterior portion in the other two patients, and all but one were located near the apex.

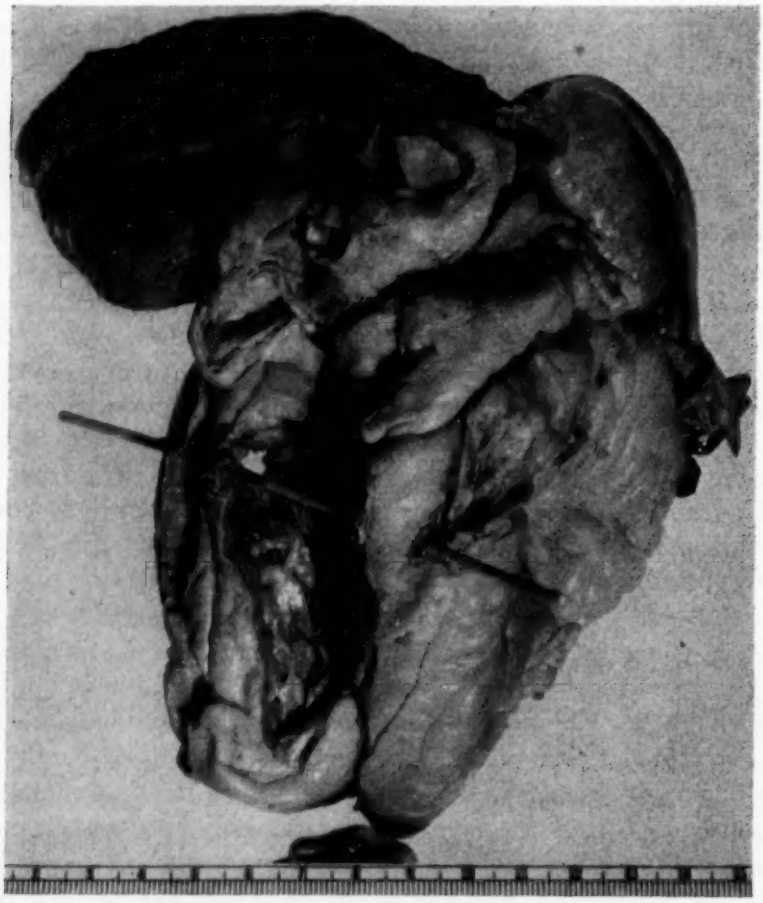

Fig. 1.—Case 8, M. H. Posterior view of heart showing right ventricular side of septal perforation and smaller perforations in the posterior wall of the right ventricle.

The size of the perforation may vary greatly. In the cases just presented, they ranged from the diameter of a probe to 4 cm. Likewise, the number of perforations is subject to some variation. Although the majority of cases show just one perforation, six cases have been reported with multiple perforations. The most unusual case in this respect contained nine separate defects, measuring from 2 to 5 mm. in diameter.[7]

The combination of rupture of the free ventricular wall and perforation of the interventricular septum is a rarity. It has, however, occasionally been reported.[25,26] Two of the patients in this series, C.T. and M.H., are examples of this unusual combination, and in both cases, the immediate cause of death was cardiac tamponade. A perforation through the base of the septum was combined with a 1 cm. tear through the anterolateral wall of the left ventricle in one patient, while in the other patient, a perforation through the upper posterior portion of the septum extended into and through the posterior wall of the right ventricle (Figs. 1 and 2). This is particularly unusual since perforations through the pos-

Fig. 2.—Case 8, M. H. Same heart showing left ventricular side of septal perforation.

terior wall of the right ventricle are extremely rare. Edmondson and Hoxie,[11] in a series of seventy-two cases of rupture of the heart, found ruptures in every portion of the myocardium except the posterior wall of the right ventricle.

Differential Diagnosis.—The sudden appearance of a systolic sound shortly following an acute myocardial infarction should suggest the following diagnostic possibilities: the rupture of a papillary muscle, a pericardial friction rub, or the development of functional mitral insufficiency. The sudden appearance of extraneous sounds or murmurs in patients with no definite evidence of myocardial

infarction suggests other possibilities, which include rupture of a congenital aneurysm of the membranous portion of the septum or of the sinus of Valsalva, rupture of a chorda tendinea, subacute bacterial endocarditis, and the rupture of a mitral or aortic valve. A congenital ventricular septal defect may also be confusing, if its presence has previously been undiagnosed.

Rupture of a papillary muscle probably presents the most difficult differential diagnostic possibility following a myocardial infarction. Brunn,[2] who made the first ante-mortem diagnosis of a perforated septum, had observed two cases of this condition. The first he had diagnosed as a ruptured papillary muscle. When autopsy proved the murmur to be due to a perforated septum, he profited by this experience and thus correctly diagnosed the next patient with the same condition.

This complication is observed somewhat less frequently than septal rupture, as only some sixty cases have been reported in the literature. However, as is true with septal perforation, this complication has been recognized more frequently in recent years. Thus, in a private hospital in Denver, three cases were observed within a fifteen-month period.[27] Like septal perforation, rupture of a papillary muscle is manifested by a sudden change in the clinical course, associated with the sudden appearance of a loud, harsh, systolic murmur.

Several clues help in differentiating this from a perforated septum.[28,29] The murmur is loudest at the apex, rather than at the left sternal border. Diastolic murmurs are more common with ruptured papillary muscles. There has never been a thrill recorded in a case of papillary muscle rupture, with the exception of one case of incomplete papillary muscle rupture,[30] while over half of the septal perforations are associated with a systolic thrill.

The electrocardiogram is frequently found helpful in this diagnostic problem. Papillary muscle rupture is usually associated with a posterior myocardial infarction, while 75 per cent of septal perforations are associated with anterior infarction. There is rarely electrocardiographic evidence of conduction defects in papillary muscle rupture, while such defects are present in 39 per cent of septal perforations. Lastly, rupture of a papillary muscle usually produces sudden left heart failure and intractable pulmonary edema, with death rapidly ensuing. With a perforated septum, heart failure usually develops more slowly, and death is often delayed a few to several days. The prognosis of a ruptured papillary muscle is worse than that of a perforated septum. Only four of sixty reported cases have survived two months, with over 50 per cent of the patients dying within the first twenty-four hours.[27]

Rupture of a mitral chorda tendinea is usually a less dramatic occurrence, seen in patients with rheumatic valvulitis, subacute bacterial endocarditis, or valvular fibrosis of unknown etiology.[30] The result is the sudden appearance of a loud, harsh, systolic murmur, best heard along the left sternal border or at the apex. A systolic thrill frequently accompanies the murmur, and occasionally a diastolic murmur may be heard. Death from congestive heart failure usually occurs, and is the result of the mitral insufficiency that has been produced. The development of congestive failure may follow abruptly, or, more often, has an insidious onset over a period of months or years.

A pericardial friction rub may be located over the left sternal border, but can usually be differentiated from a septal perforation by its auscultatory qualities, its frequent occurrence during systole, and diastole, and its transient nature. A friction rub may develop during the course of a myocardial infarction, and Bean[31] has reported an incidence of 14 per cent. Friction rubs have also been diagnosed in cases of septal perforation, occurring in two of Bond's cases and in the first case presented here. The initial "rub" in these three instances was replaced within twenty-four hours by the typical loud, blowing, systolic murmur of a septal defect.

Acute dilatation of the left ventricle produces the loud systolic murmur of mitral insufficiency. However, this murmur usually develops more slowly than the murmur of a perforated septum, is best heard at the apex, and is transmitted toward the axilla. It is usually of lower pitch and of less intensity than the murmur of a septal defect. Roentgen examination demonstrates enlargement of the cardiac silhouette, and should serial x-rays show a return of the heart to its original size, a corresponding diminution of the murmur will be noted. In Patient D. G., the onset of the murmur was associated with diffuse cardiac enlargement. However, when the heart later returned to its previous size, the murmur had not changed at all, making this diagnosis very unlikely.

Rarely, a congenital aneurysm of the pars membranacea septi may rupture, producing a murmur similar to that of a septal defect. Likewise, an aneurysm of the sinus of Valsalva can dissect down along the septum and rupture into the ventricle, producing a similar murmur. These conditions are easily differentiated from a perforated septum by the fact that they occur in young people without signs of infarction, and the murmur may be continuous in nature.

Bacterial endocarditis, acute or subacute, may produce a variety of different types of murmurs. Occasionally, it can also produce a perforation of the interventricular septum with its characteristic murmur.[32] This should present little diagnostic difficulty because of the concomitant presence of other signs of bacterial endocarditis.

A diseased mitral or aortic cusp, and occasionally even a normal cusp, may rupture with the sudden appearance of a new murmur. There is an early, loud, diastolic murmur heard in the aortic area when this valve is ruptured. There is also an increased pulse pressure resulting from the aortic insufficiency. These conditions are not associated with infarction.

A congenital ventricular septal defect usually occurs in the membranous portion of the septum, and its murmur is also best heard in the fourth intercostal space along the left sternal border. Should the patient be observed for the first time following an acute myocardial infarction, and the characteristic systolic murmur be present at this time, as in patients C. H. and J. D., differentiation would be difficult. However, the finding of a congenital septal defect in this age group is so unlikely that it should present no real problem.

The 68-year-old patient, D. G., who is still living nine months after his infarction, presents an interesting problem in differential diagnosis. Five days after an extensive anterolateral infarction, there suddenly appeared the typical murmur of a septal perforation along the left sternal border. Although a septal perforation was the first impression, other possibilities were a ruptured papillary

muscle, a pericardial friction rub, or acute cardiac dilatation. A friction rub can be eliminated by the fixed nature of the murmur and its blowing quality. Cardiac dilatation was ruled out when x-rays showed a decrease in heart size, while the murmur remained constant. Militating against a ruptured papillary muscle are the location of the murmur and the fact that the infarction was anterolateral and not posterior in location, and finally, that the patient is living nine months later.

Cardiac catheterization was performed in this patient six months after his myocardial infarction in an attempt to establish a definitive diagnosis. The only positive findings were increased pressures within the right ventricle, (75/08 mm. Hg), and pulmonary artery (75/40 mm. Hg). The pressure in the right auricle was 15/10 mm. Hg with prominent A/waves, and the pressure tracing revealed no evidence of tricuspid insufficiency. Peripheral arterial saturation studies were normal as the brachial artery saturation was 94.3 per cent. Although a left-to-right shunt was not demonstrated, it is still considered that a small septal defect is the most likely explanation for the murmur. The amount of blood shunted across the defect could be so small as to escape detection by the methods employed. An additional factor that might decrease the volume of the left-to-right shunt could be the considerable degree of pulmonary hypertension detected at the time of catheterization. Other cases of congenital interventricular septal defects have been seen where, clinically, the diagnosis seemed apparent, and yet saturation studies were normal. It was felt that these were also cases of very small shunts, too small to be detected by the methods used.[33-35]

Few patients survive a septal perforation following a myocardial infarction. However, in those who do survive, a definitive diagnosis can only be established by the use of cardiac catheterization. Diagnosis is important in these cases because the recent advances in cardiovascular surgery make the closure of such a defect not beyond the realm of possibility.

SUMMARY

Eight cases of ventricular septal perforations are presented, and the present literature, consisting of 132 cases, is reviewed.

The diagnosis of this condition should be strongly considered when a patient with an acute myocardial infarction suddenly develops a blowing systolic murmur along the lower left sternal border. Recognition is of importance in a consideration of the prognosis, as less than 10 per cent survive one year.

In one patient, cardiac catheterization was performed in an attempt to confirm the diagnosis, and in two patients the unusual combination of a ruptured septum and a ruptured ventricle was present.

The differential diagnosis has been discussed, with particular attention to the differentiation of septal perforation from papillary muscle rupture.

SUMMARIO IN INTERLINGUA

Es presentate octo casos de perforation del septo interventricular. Nos passa in revista le litteratura nunc existente que consiste de 132 casos.

Le diagnose de iste condition deberea esser considerate multo seriemente quando un patiente con un acute infarcimento myocardial disveloppa subitemente un sufflante murmure systolic al longo del margine sternal sinistro-inferior.

Le recognition del condition es importante pro le prognose: minus que 10 pro cento del patientes supervive plus que un anno.

In un patiente, catheterisation cardiac esseva executate pro confirmar le diagnose. Duo patientes habeva le combination inusual de ruptura septal con ruptura ventricular.

Es discutite le diagnose differential. In isto attention special es prestate al differentiation de perforation septal ab ruptura de musculo papillar.

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DISTENSIBILITY OF THE PULMONARY ARTERIAL VESSELS AT REST AND DURING EXERCISE IN PATIENTS WITH MITRAL STENOSIS

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THE rise of systolic, diastolic, and mean pressure within the pulmonary artery during exercise in patients with severe mitral stenosis is a well-documented observation. An analysis of the behavior of the pulmonary arterial pulse pressure, i.e., the systolic-diastolic pressure difference, and the stroke volume in these patients reveals a particular type of response from which certain deductions may be made regarding the distensibility of the pulmonary arterial bed, in these circumstances. The observation is that pulmonary arterial pulse pressure has increased during exercise at the time when stroke volume almost invariably has decreased from the resting level. The decreased stroke volume results from the disproportionate rise of heart rate as compared with cardiac output. This pattern of events can be found in the published reports of patients studied by various investigators: Cournand and collaborators,[1] Eliash, Wade, and Werko,[2] and Bing and associates,[3] to mention several of the larger series. It is not peculiar to one laboratory or to one type of transducing and recording apparatus. The observation of this reciprocal relationship between two measurements, pulse pressure and stroke volume which usually vary directly with one another, suggests the possibility that, with the rise of pulmonary arterial pressure which occurs in patients with mitral stenosis during exercise, the pulmonary arterial wall becomes more resistant to stretch, and the arterial cylinder less distensible, thus accepting the systolic inflow from the right ventricle only under the insistence of a higher lateral pressure.

An analogous situation may be found in the systemic circuit where wide pulse pressures are found in the presence of systemic arterial hypertension. This has been considered to be the result of a decrease in the arterial distensibility from that which pertains at normal levels of arterial pressure.[4] Similar widening of aortic pulse pressure has been observed with aging and in the presence of atherosclerosis.[4]

It is the purpose of this communication to direct attention to the occurrence of this decreased distensibility in the pulmonary circulation in mitral stenosis, to indicate the significance of this property of arterial vessels in the determination of systolic and diastolic pressure within the pulmonary arterial bed, and to attempt a rough quantitation of the degree of alteration in distensibility.

From the type of analysis which has been undertaken here, it is not possible to determine the physiologic factors responsible for the altered elastic properties of the arterial wall. The mechanism may be either an active one involving

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vasomotor activity, or a passive one wherein the arterial wall becomes increasingly rigid or less stretchable as a consequence of the increased internal distending pressure which prevails during exercise in these patients. That the latter effect is a fundamental property of arterial tissue, including that of the pulmonary artery, was first shown by Roy in 1880,[5] and confirmed by other investigators since.[6-9]

We have attempted to assign some magnitude to the factor of distensibility by use of the formula proposed by Deuchar and Knebel in 1952.[10] The equations used by them were adapted from those which had been developed by Otto Frank[11] and Broemser and Ranke[12] to describe, in mathematical terms, the determinants of systolic and diastolic pressure within a system of elastic tubes subjected to periodic, rapid fluctuation in volume. By application of the physical principles regarding viscous flow to this particular context, Frank, in 1899,[11] set up his "Compression Chamber," or "Windkessel" theory of arterial function. The arterial portion of the vascular bed was visualized as a chamber whose elastic walls expanded to accommodate the systolic discharge of the ventricle. Subsequent contraction of the walls during diastole moved blood through the vascular system at a rate varying directly with the pressure head and inversely with the resistance offered to flow. Equations were developed to describe the relationships between systolic and diastolic pressure within the "Windkessel," its distensibility and the stroke volume, duration of systole and diastole, and the resistance to efflux from the chamber. One purpose of this approach was to develop a means of predicting stroke volume from systolic, diastolic, and pulse pressure with its obvious applications to physiologic experimentation. In order to accomplish this, it was necessary to know the change in pressure per unit change in volume, that is, the coefficient of elasticity of the particular system under study. It was at this point that such attempts at prediction lost their accuracy inasmuch as no satisfactory method could be found to predict elastic behavior. The inadequacies of this approach were shown in a series of papers by Hamilton and Remington.[13]

The advent of cardiac catheterization made it possible to measure stroke volume, heart rate, resistance to flow, and systolic and diastolic pressure directly in man. It became possible, thereby, to utilize these previously derived equations, not for the purpose for which they were originally intended, but for the calculation of the elasticity of the arterial compression chamber.

The measure of elasticity which has been calculated is what may be called an effective volume elasticity coefficient, termed E′, for the pulmonary arterial compression chamber. This is defined as the ratio of change in pressure to absolute increment of volume.

$$E' = \frac{\Delta P}{\Delta v}$$

This term E′, then, is the reciprocal of the distensibility and larger values of E′ will indicate decreases of distensibility.

The particular equation used to assess the magnitude of the term E′ is a modification of one of the relationships proposed by Broemser and Ranke[12] in 1930.

$$W = E' \frac{Pd}{Ps - Pd} \frac{DD}{} \quad (1)$$

where

W = resistance to outflow from the Windkessel
E′ = volume elasticity coefficient
DD = duration of diastole in seconds
Ps = systolic pressure in dynes/cm.²
Pd = diastolic pressure in dynes/cm.²

For a detailed discussion of the experimental background of this particular formulation, the reader is referred to the original paper on the subject.[12]

The term "W" has been considered by us to represent the "total pulmonary cardiovascular resistance to flow," including that offered by the mitral valve. It is felt that the stenosed valve is simply another resistance in series with that offered by arterioles, capillaries, and pulmonary veins. "W" would thus be measured by the gradient between pulmonary arterial mean pressure and the left ventricular mean diastolic pressure (Pdlv), as follows:

$$W = \frac{Pm - Pdlv}{C.O.} \quad (2)$$

where C.O. = cardiac output in cubic centimeters per second.

In equation 1, in place of "Pd" in the numerator (which is taken as the driving force during diastole), we have substituted a somewhat more realistic value which is the pressure gradient between an estimated pulmonary arterial mean diastolic pressure (Pdm) and left ventricular mean diastolic pressure (Pdlv).

Substituting for the two terms "W" and "Pd" in equation 1 and solving for E′, the equation which has been used for calculation appears as follows:

$$E' = \frac{(Pm - Pdlv)}{(Pdm - Pdlv)} \frac{(Ps - Pd)}{DD\ C.O.}. \quad (3)$$

All values are in C.G.S. units and, therefore, pressure terms are expressed in dynes/cm.² duration of diastole in seconds, and cardiac output in cubic centimeters per second. The effective volume elasticity coefficient (E′) is in terms of dynes/cm.⁵

Since left ventricular diastolic pressure cannot be determined by right heart catheterization, it is at this point that a basic assumption must be made. This assumption is that the left ventricular diastolic pressure does not change with exercise. The reasons for believing this to be a valid assumption in this particular group of patients will be detailed later. It is also necessary to assign some arbitrary value to this pressure. Inasmuch as primary interest in this report has been focused on changes in elasticity induced by exercise in each individual, with less significance attached to absolute values, the arbitrary value assigned to the left ventricular diastolic mean pressure is of less importance than the assumption that this value is the same at rest as during exercise. A value of 5 mm. Hg has been assigned to the mean left ventricular diastolic pressure. This value is the same as that employed by Gorlin and associates[14] in calcuations of mitral valve area, and has been found in our laboratory to approximate rather closely the actual

values observed in patients with mitral stenosis when pressures are obtained during mitral valve surgery.[15] A second basic assumption is that the determination represents a steady state wherein the outputs of the left and right ventricles are equal. Finally, in so far as could be determined clinically and at operation, no patient had any other significant valvular lesion; in particular, mitral insufficiency, pulmonary insufficiency, or aortic stenosis or insufficiency. The presence of dynamically significant lesions of this type render the calculations invalid.

This adaptation of the original expression to the present purpose rests on the premise that resistance to flow per cubic centimeter of blood per second is the same at levels of mean diastolic pulmonary arterial pressure as at levels of mean pulmonary arterial pressure. This relationship is revealed if one considers that

$$E' = \frac{\Delta P}{\Delta v}$$

The change in pressure during cardiac ejection (ΔP) is represented by Ps-Pd. The net increase in the volume of the pulmonary arterial compression chamber during the cardiac cycle responsible for that increase in pressure is the quantity remaining within the chamber at the end of systole. This quantity is equal to the stroke volume minus the volume of blood which drained out into the venous bed during systole. The net volume remaining at the termination of systole is then equal to the blood flow during diastole.

Thus,
$$E' = \frac{\Delta P}{\Delta v} = \frac{Ps - Pd}{\text{diastolic drainage}}$$

Substituting the latter expression for E′ into equation 3 yields the two resistance terms described above:

$$\frac{(Pm - Pdlv)}{C.O.} = \frac{(Pdm - Pdlv)\ DD}{\text{diastolic drainage}}$$

This is obviously a considerable simplification, and the value of E′ which has been calculated, therefore, will differ quantitatively from the true value of the elastic coefficient in three ways.

1. Resistance to flow actually may vary inversely with the level of internal distending pressure due to larger vessel diameter at higher values than at lower ones. Resistance would thus be less at levels of mean pressure than at mean diastolic pressure. The present calculation of E′ would be greater than the true value according to the influence of this effect.
2. The value for pulse pressure (Ps-Pd) has been used to represent the quantity ΔP. The true distending pressure corresponding to the distending volume represented by the diastolic efflux (Δv) is in reality the difference between incisural pressure and diastolic pressure (Pi-Pd). Again, the calculated E′ will be larger than the true value by the ratio $\frac{Ps - Pd}{Pi - Pd}$

3. The assumed value for left ventricular mean diastolic pressure may vary from one individual to another.

However, the simple formulation proposed has the advantage of being readily measurable as a clinical approximation and of indicating the marked directional changes which have taken place.

MATERIAL AND METHODS

All (10) patients were from ward and private services of The Mount Sinai Hospital, and studies were carried out by the Cardiac Catheterization Group under the direction of Dr. A. J. Gordon. Strain gauges were employed as pressure transducers and records were obtained with a four-channel oscillographic recorder. Blood samples for oxygen content were obtained simultaneously from the pulmonary artery and brachial artery for cardiac output determination. Oxygen consumption was determined in most cases by collection of expired air in a Tissot spirometer, and analysis of the gas content in a Scholander microgas analyzer. The respiratory quotient was calculated on these determinations in order to insure the presence of a steady state. On some occasions a modified 9 litre Benedict-Roth spirometer was used in measurement of oxygen consumption. Determinations were done at rest and during the eighth to twelfth minute of steady state exercise which consisted of pedaling a stationary bicycle while in the supine position. All of the patients reported were observed at operation, and the diagnosis of mitral stenosis without observable regurgitation was sustained in all. On clinical examination, no patient was found to have complicating lesions of the aortic valve, and in no case was a Graham-Steell murmur of pulmonary regurgitation of more than the faintest audible intensity present. All patients but one had regular sinus rhythm, and all were women. None were in congestive failure at the time of study, though several had been decompensated in the past. Measurements of systolic and diastolic pressure were made in the usual fashion. Mean pressure was determined electronically at the time of recording. Pulmonary arterial mean diastolic pressure was estimated as end diastolic pressure plus one-half the difference between end diastolic pressure and mean pressure. This estimation was adopted because of the difficulty of obtaining adequate planimetric measurement of mean diastolic pressure from many of the curves. The duration of diastole was measured from the pulmonary artery curves.

RESULTS

Table I, which contains all of the hemodynamic information, has been arranged in order of increasing values of the resting elasticity coefficient. The range of individual values of E′ is wide, from 528 dynes/cm.^{5} to 3590 dynes/cm.^{5} at rest and from 914 to 12,300 dynes/cm.^{5} on exercise. It is apparent that the level of E′ increased in each subject studied, though the degree of change varied widely among individuals. The average of the ratios of "E′ exercise/E′ rest" is 2.48. All patients showed elevated resting pulmonary arterial mean pressure and all sustained a rise upon exercise. Pulse pressure increased on

TABLE I

NO.	SEX	AGE	RHYTHM	Pm	Ps	Pd	P.P.	DD	CL	CARDIAC OUTPUT*	SV	E′	Δ E′ / Δ Pm	MVFR	W
1															
Rest	F	32	RSR	28	36	21	15	.52	.76	5,160	65.3	528		9,940	356
Exercise				46	65	30	35	.32	.56	5,720	53.5	1,910	172	17,800	574
2	F	42	RSR	18	32	13	19	.6	.91	4,600	69.7	683		7,600	226
				23	41	17	24	.44	.72	4,300	51.8	1,220	107	9,760	334
3	F	29	RSR	35	43	26	17	.44	.80	6,120	81.5	595		13,900	392
				53	79	41	38	.36	.64	7,040	74.8	1,370	43	19,500	545
4	F	31	RSR	24	31	17	14	.36	.64	4,700	50	810		13,000	324
				32	44	28	16	.28	.56	4,900	55	914	13	17,500	366
5	F	36	RSR	33	48	29	19	.36	.62	5,180	53.4	876		14,400	432
				52	70	35	35	.28	.56	6,670	62.3	1,850	51	23,800	565
6	F	32	RSR	36	42	26	16	.42	.59	2,970	29.4	1,215		7,100	835
				58	85	40	45	.23	.38	3,640	23.2	5,150	179	15,800	1,160
7	F	34	RSR	36	53	23	30	.36	.64	7,040	75	1,200		19,500	352
				50	74	34	40	.28	.52	7,480	65.7	1,860	47	26,800	482
8	F	30	RSR	46	59	36	23	.32	.56	4,450	41.6	1,470		13,900	737
				61	92	51	41	.22	.38	4,480	29.4	3,650	145	20,400	998
9	F	39	AF	51.5	81	31	50.2	.56	.8	3,940	52.5	2,320		7,030	941
				73.6	120	41.5	78.5	.46	.64	3,440	36.7	5,250	133	7,500	1,590
10	F	32	RSR	57	78	41	37	.36	.6	2,700	27	3,590		7,500	1,535
				102	138	72	66	.20	.42	2,500	17.5	12,300	193	12,500	3,090

Pm = Pulmonary arterial mean pressure. Ps = Pulmonary arterial systolic pressure. Pd = Pulmonary arterial diastolic pressure. P.P. = Pulmonary arterial pulse pressure. DD = Duration of diastole in seconds. CL = Duration of cycle length in seconds. SV = Stroke volume. E′ = Volume elasticity coefficient. MVFR = Mitral valve flow rate in cubic centimeters per minute of diastole. W = "Total cardiopulmonary resistance."

*Cardiac output in cubic centimeters per minute.

exercise in each patient, while stroke volume decreased in all but two of the patients. Heart rate increased with exercise in all patients as shown by the decreased time of the cycle length and the duration of diastole likewise decreased. Cardiac output declined during exercise in three of the ten patients and rose by a small amount in the other seven. Total pulmonary resistance increased in all patients, though the change was not extensive. Mitral valve flow rate per minute of diastole increased significantly in all but two patients.

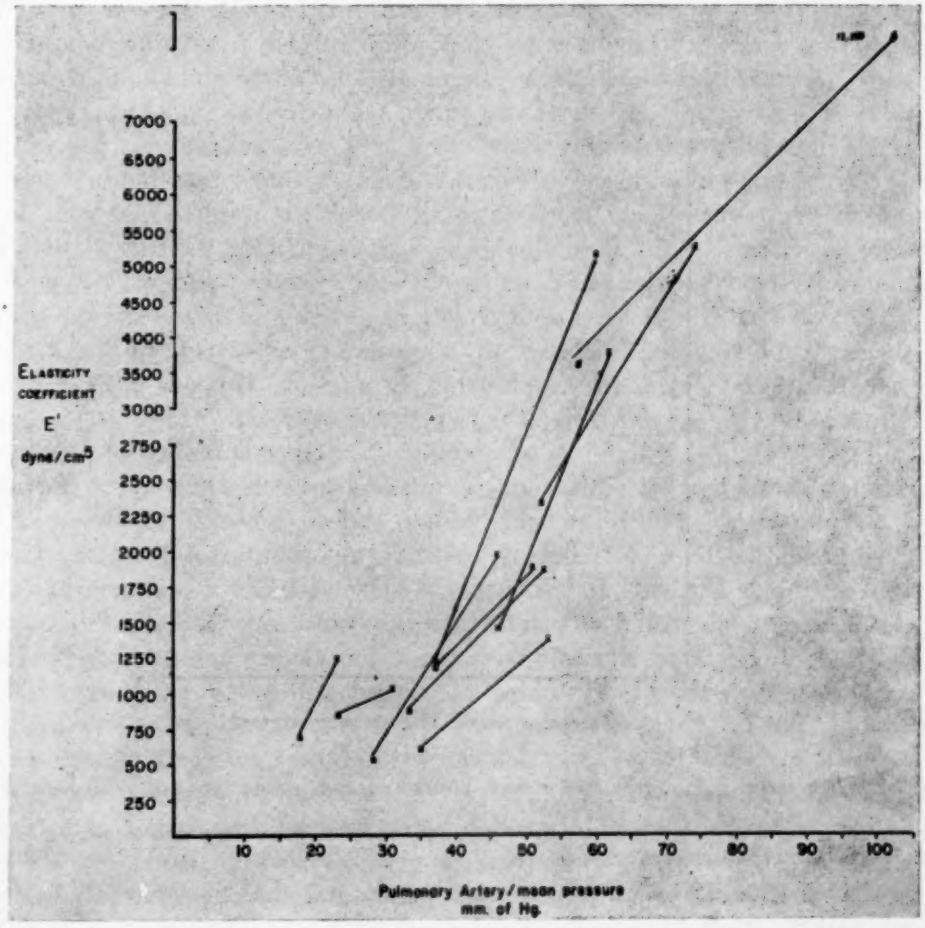

Fig. 1.—The relationship of the volume elasticity coefficient (E′) to pulmonary arterial mean pressure during rest and exercise is shown for each individual study. Exercise has resulted in a rise in pulmonary arterial mean pressure and E′ in all studies.

Of all of the above-mentioned hemodynamic changes which have occurred during exercise, the rise in pulmonary arterial mean pressure has been found to correlate most closely with the increase in the coefficient of elasticity. In Fig. 1, the level of E′ is plotted against mean pressure for each individual patient during rest and exercise. Though a straight line has been drawn between the rest and exercise values, it is not meant to imply that the curve of E′ against Pm is a

linear one, or that intermediate points are determinable from only two values. An indication that the relationship is probably not linear is seen in Fig. 2. Here the ratio $\frac{\Delta E'}{\Delta Pm}$ has been plotted against pulmonary arterial mean pressure at rest for each patient studied. It can be seen that the change in E′ during exercise per unit change in mean pressure is more extensive when absolute levels of the latter are high than when they are in the normal range, or only moderately elevated. It might be predicted, then, that the curve of the elastic coefficient when plotted against mean pressure would progressively incline toward the Y axis at higher levels of mean pressure.

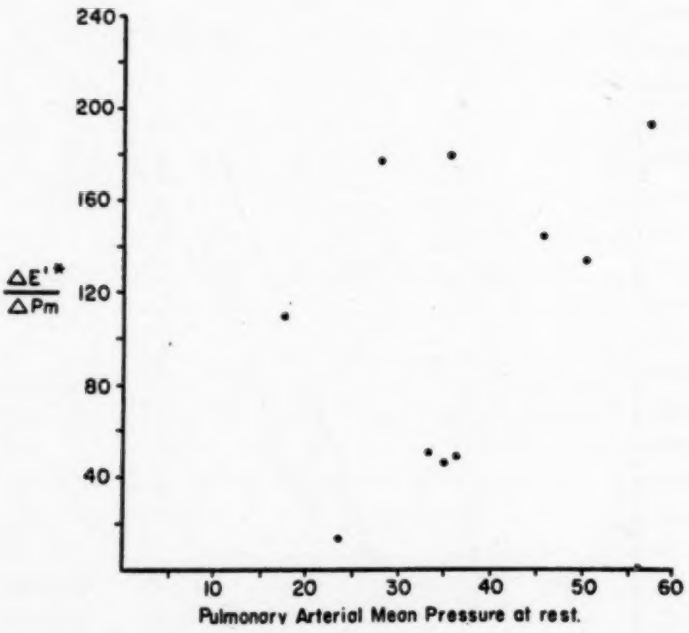

Fig. 2.—The ratio $\frac{\Delta E'}{\Delta Pm}$ during exercise is plotted against resting levels of pulmonary arterial mean pressure. Note that the increment in E′ per unit change in Pm during exercise is greatest when resting levels of Pm are highest.

There is a little relationship between absolute values of the "total pulmonary cardiovascular resistance" (W) and the elastic coefficient, though in general those patients with the very highest values of E′ also had high values of "W." The average of the ratios "W exercise/W rest" is 1.47.

There was no observable relationship between E′ and cardiac output, stroke volume, duration of diastole, or heart rate either at rest or during exercise. It was felt, therefore, that the coefficient of elasticity did not limit these variables in the patients who were studied, nor was the magnitude of the change of any of these factors a significant contributor to the magnitude of E′.

DISCUSSION

In the foregoing analysis, we have attempted to demonstrate that the volume elasticity coefficient of the pulmonary artery increases during exercise in patients with mitral stenosis, and that this change accompanies the rise in pulmonary arterial mean pressure. This would explain the observation that pulse pressure has increased during exercise, while stroke volume has fallen. The type of calculation employed shows only that there is increased force necessary to expand the walls of the arterial cylinder to accommodate a unit volume increase during cardiac ejection. However, the total volume of the arterial bed into which this unit volume is injected is not known, nor is the effect of exercise upon this end diastolic volume known. Without a direct knowledge of this quantity the actual basic elastic behavior of the walls cannot be calculated, for, though we refer to a coefficient of volume elasticity, it is actually the resistance of the walls to circular and longitudinal elongation which is observed. It is obvious, then, that the injection of a unit volume of blood into a vessel of small radius will stretch the arterial walls further than the same volume injection into one with larger radius, and if the elastic response per unit elongation is the same in both, the change in internal pressure will be greater in the former than in the latter. Thus it is conceivable that the rise in E′ observed during exercise might be the result of a decrease in the diastolic volume of the pulmonary arterial bed. One is then obliged to postulate that exercise, in patients with mitral stenosis, results in a decrease in the pulmonary arterial volume and since pulmonary arterial diastolic pressure is observed to rise during exercise, that an active vasoconstriction of the large arterial branches has taken place. This type of behavior has not been generally attributed to pulmonary arterial vessels inasmuch as their walls do not have an appreciable muscular coat. It is felt that the occurrence of the sequence of events described above is unlikely and that it is more probable that exercise results in an increase in the pulmonary arterial diastolic volume. The elevation of diastolic pressure and the increase in the elastic coefficient during exercise can then be explained as simple physical consequences of the increased diameter of the vessels and increased tension of the walls.

This latter explanation is in accord with the observation made in vitro by a number of investigators[5-14] on all types of arterial vessels, namely, that as the vessel wall is stretched, it increasingly resists further stretching. In this, arterial tissue differs from metal wherein the degree of lengthening is proportional to the force applied. That this is true of the pulmonary artery as well as the systemic arteries was pointed out by Roy,[5] in 1880, and Hochrein,[6] in 1927. The latter stated that at comparable degrees of tension, strips of pulmonary artery actually were more resistant to stretch than strips of aorta. An explanation of this elastic behavior has been discussed by Burton[16] and is possibly applicable here. The vessel walls contain variable degrees of muscle, elastic fiber, and collagen. The resistance to stretch of the collagen is several hundred times as great as that of the elastic fiber and muscle. Over the lower ranges of internal pressure the vessel responds to stretch with the response of its elastic fibers, the collagen remaining unstretched. However, with a rise in internal pressure, sufficient extension of the wall occurs, the collagen fibers are put on stretch, and the response of the

vessel to further increase of volume will be that of these relatively nondistensible tissues. Thus, small increments of volume will be achieved only at the expense of large increases in internal pressure. This point is illustrated in Fig. 2 of this study. If the pulmonary artery mean pressure may be considered to roughly reflect the tension of the vessel wall, it may be seen that the increase in E′ per unit increase in pulmonary arterial mean pressure during exercise is greater when the resting values are already high than when they are low, i.e., when the walls are already stretched to a greater extent. Since the decrease in distensibility observed during exercise in these patients is similar to that observed in normal arterial segments which have been subjected to stretch, it is not possible to state whether the response observed here is quantitatively or qualitatively different from normal tissues. To determine whether the rheumatic process or chronic pulmonary hypertension had wrought specific changes in the pulmonary arterial wall, it would be necessary to compare the values of E′ observed here with those derived from "normal" individuals subjected to a similar elevation of pulmonary arterial pressure or pulmonary diastolic blood volume. This cannot be accomplished in vivo and it is likely that only studies of pulmonary arterial segments excised at post-mortem examination will give information on this point. Calculations of the magnitude of the elasticity coefficient at rest in the average normal individual with a pulmonary arterial mean pressure of 13 mm. Hg, systolic pressure of 23 mm. Hg; mean diastolic pressure of 10 mm. Hg, cardiac output of 6000 c.c. per minute, and duration of diastole of 0.6 second yields a value of about 360 dynes/cm.[5]

We have not included calculations of the effect of exercise upon the values of E′ in normal individuals. It is felt that these would be less valid than those reported here because the absolute levels of pressure are lower and thus very small measurement variations of 1 to 2 mm. Hg make highly significant alterations in the calculations, whereas this is not as true when pressure levels are higher. Moreover, the assumed value of 5 mm. Hg, as representing left ventricular mean diastolic pressure, may actually be as large as pulmonary arterial mean diastolic pressure, or be such a considerable fraction of it as to render any calculations meaningless.

As mentioned previously, in order to arrive at a value for resistance to flow in the pulmonary circuit in mitral stenosis, it was necessary to assume an arbitrary value for left ventricular diastolic pressure, and to assume that this changed little, if at all, with exercise. The assumption that there is no increase in the left ventricular diastolic pressure with exercise can be validated only by inference, as there are no comparable experimental data in animals or humans on the behavior of left ventricular diastolic pressure during exercise. The behavior of the normal left ventricle is probably analogous to that of the right ventricle, which has been shown to respond to exercise by slight, if any, increase in diastolic pressure, even though stroke volume may increase considerably. All patients with mitral stenosis studied here were found to be without any evidence of left ventricular enlargement and none were believed to have active rheumatic carditis at this time. Thus it is likely that the performance of the left ventricle during exercise was not different from that of normal individuals. The second reason for be-

lieving that the left ventricular diastolic filling pressure did not rise during exercise was that stroke volume almost uniformly decreased. In a competent ventricle, without pericardial constriction, a decrease in stroke output is attended by constant or slightly decreased diastolic filling pressure. Finally, in support of the assumption of the adequacy of left ventricular function in these patients during exercise, it can be stated that no patient was selected with evidence of aortic insufficiency or stenosis; the absence of mitral insufficiency was confirmed at operation in all patients. The presence of mitral insufficiency will result in underestimation of the degree of mitral valve flow, total pulmonary cardiovascular resistance to flow, and the volume elasticity coefficient. Pulmonic regurgitation was not felt to be dynamically significant in the resting state, or on exercise in any instance. However, by reduction of diastolic pressure and widening of pulse pressure, pulmonary insufficiency may simulate changes in distensibility.

The significance of the increased coefficient of elasticity of the pulmonary artery lies in the effect upon the work required of the right ventricle. Greater pressure energy must be imparted to the blood stream by the ventricle, merely to expand the arterial walls sufficiently to accommodate the systolic discharge, than would be necessary at comparable degrees of mean pressure in the presence of less rigidity.

CONCLUSIONS

A decrease in the distensibility of the pulmonary arterial tree has been demonstrated to occur during exercise in patients with mitral stenosis. This alteration in the elastic properties of the vascular wall accompanied the rise in pulmonary arterial mean pressure which occurred during exercise in the patients who were studied, and explained the observation that pulmonary arterial pulse pressure increased during exercise even though the stroke volume had decreased. A rough quantitation of this physical property has been attempted by calculation of an effective volume elasticity coefficient. The decrease in distensibility is believed to be a passive consequence of an increase in the pulmonary arterial volume and vessel diameter. This explanation would accord with the known elastic response of blood vessels to stretch or distension. Inasmuch as decreased vascular distensibility results in a higher systolic pressure at the same level of stroke volume, heart rate, etc., more cardiac work is required of the right ventricle to expand the arterial walls sufficiently to accommodate the stroke volume than would be necessary if distensibility had not altered during exercise.

SUMMARIO IN INTERLINGUA

Esseva demonstrate que un reduction del distensibilitate del arbore de arterias pulmonar occurre durante exercitio in patientes con stenosis mitral. Iste alteration del proprietates elastic del pariete vascular accompaniava le augmento del pression pulmono-arterial median que occurreva durante exercitio in le patientes studiate e explicava le observation que le pression de pulso pulmono-arterial se augmentava durante le exercitio ben que le volumine per pulso se habeva reducite. Un quantitation approximative de iste proprietate physic

esseva essayate per le calculation de un coefficiente de elasticitate del volumine. Le reduction del distensibilitate es considerate como un consequentia passive de un augmento del volumine pulmono-arterial e del diametro vascular. Iste explication esserea de accordo con le cognoscite responsa elastic de vasos sanguinee a tension o distension. Proque le reducite distensibilitate vascular resulta in un plus alte pression systolic con non-alterate nivellos de volumine per pulso, rapiditate cardiac, etc., le labor requirite ab le ventriculo dextere pro extender le pariete arterial in le mesura correspondente al augmentate volumine per pulso es plus grande que si le distensibilitate non habeva essite alterate durante le exercitio.

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MILD COARCTATION OF THE AORTA WITH NORMAL BLOOD PRESSURE

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COARCTATION of the aorta is usually considered to be accompanied by hypertension in the upper extremities and this generally is true. Steele,[1] in 1941, reviewed 217 cases of coarctation and found that almost all showed systolic hypertension and almost one-half had a diastolic pressure of over 100 mm. Hg. However, King,[2] in 1937, found 170 cases of coarctation of the aorta in which the blood pressure was recorded, in nineteen of which the blood pressure was normal. The incidence of normal blood pressure in coarctation is probably much higher, as there has been a tendency to omit mild cases of coarctation from case reports or reviews of autopsy material. The view has generally been taken that mild cases of coarctation of the aorta are of no clinical importance because the patients do not die of the usual results of coarctation; namely, congestive heart failure, cerebral hemorrhage, or rupture of the aorta. However, there is one other complication to which it is probable that even the mild cases of coarctation are as susceptible as the severe ones; namely, bacterial endarteritis and subacute bacterial endocarditis engrafted upon a bicuspid aortic valve. That this may occur was shown by a patient of Hallock and Hebbel,[3] in 1939, whose death was due to subacute bacterial endocarditis on a bicuspid aortic valve associated with mild, nonclinical coarctation. Reifenstein, Levine, and Gross,[4] in 1947, reviewed 104 autopsied cases of coarctation in patients over 2 years of age and found that a bicuspid aortic valve was associated with coarctation in 42 per cent of the cases, and that death due to subacute bacterial endocarditis on this valve plus bacterial endarteritis of the aorta accounted for 23 per cent of deaths. In their series the blood pressure was recorded in seventy-four cases and was found to be normal in five instances. When to this is added the probability that many mild cases of coarctation are misdiagnosed as other forms of heart disease and perhaps unduly limited in their physical activity, the importance of the recognition of mild cases of coarctation becomes apparent.

Our purpose in this paper is not to present new or different material, since many other observers have called attention to the possible existence of a normal blood pressure in coarctation, but rather to re-emphasize the failure of coarctation of the aorta with normal blood pressure. Clinical and physiologic studies are

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presented on six young adult men with normal brachial artery pressures as determined by direct intra-arterial measurement and in whom the diagnosis of coarctation of the aorta seems established. Three of the cases probably should be considered subclinical and three were severe enough to be considered candidates for surgical correction. All had been examined on several occasions prevously and in none was the patient aware of the diagnosis.

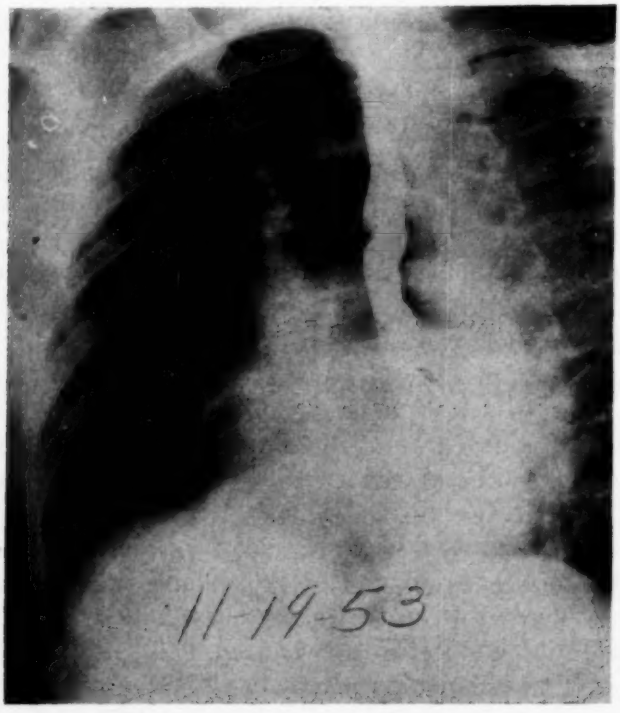

Fig. 1.—Left anterior oblique view with barium swallow from Case 4. Note that poststenotic dilatation of the aorta has displaced the esophagus.

MATERIAL

Six young adult men 19 to 29 years of age were studied mainly because of the presence of a systolic murmur. Five were in the military service and one was an applicant for appointment to the United States Military Academy. All considered themselves be to in good health and coarctation of the aorta was suspected because of the presence of a murmur discovered on routine physical examination. In only one instance (Case 1) were any symptoms present and his complaint was "palpitation." In three cases estimation of the blood pressure in the arms by sphygmomanometry was above normal with the typical murmur being present, and in three cases a normal blood pressure was recorded and the major clue to the condition on physical examination was the presence of a Grade 2 to 3 systolic murmur which was maximal beneath the sternum at the level of the second to the fourth intercostal spaces and usually heard in the back. In all

cases (except Case 3 where the systolic pressure was 155) the brachial artery pressure by direct measurement was normal. By palpation the femoral artery pulsations were considered normal in one case (Case 3), slightly decreased in one case, decreased in three cases, and "feeble" in one case (Case 6). Evidence for collateral circulation as shown by physical examination or by notching of ribs as seen on the roentgenogram was present in four of the six cases. Poststenotic dilatation, as demonstrated best by x-ray studies of the chest in the left anterior oblique view with barium swallow (Fig. 1) was present in all cases, and in two instances the area of coarctation could be seen on the plain posteroanterior

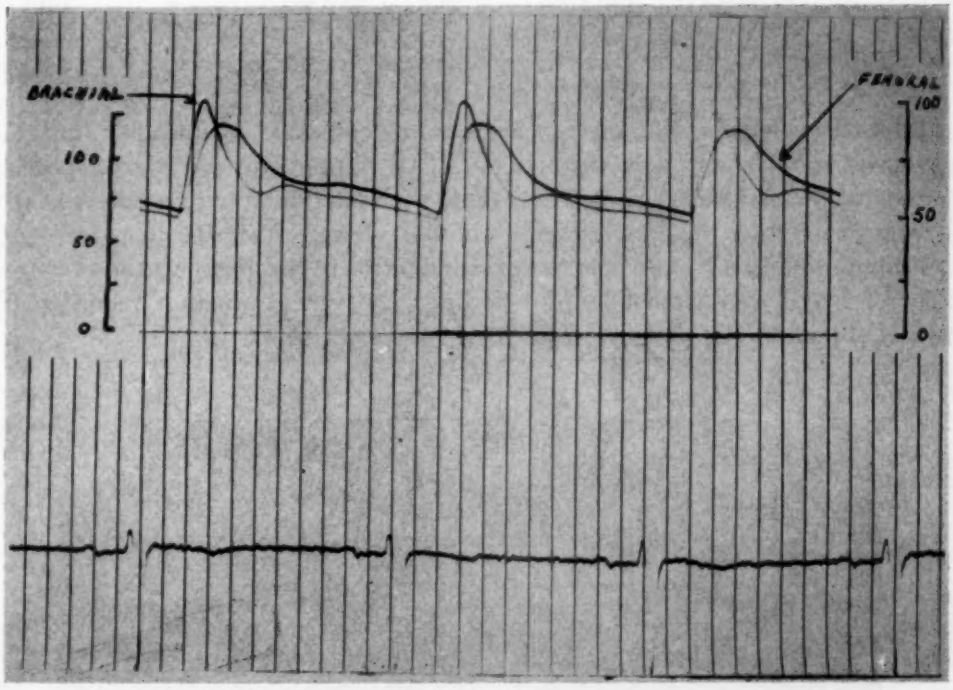

Fig. 2.—Simultaneous recording of right brachial and femoral artery pulse tracing from Case 1.

chest roentgenogram. The heart size was normal by x-ray in three cases and slightly enlarged in three. Incidentally, the cardiac enlargement was present in Cases 4, 5, and 6, which had shown some systolic or diastolic blood pressure elevation by sphygmomanometry. The electrocardiogram was normal in five cases and showed left ventricular hypertrophy in Case 6. Data are shown in tabular form in Table I.

METHODS

Needle puncture of the right brachial and femoral arteries were performed and Hathaway recording apparatus used to record the simultaneous pressures and characteristics of the pulse curves. (See Fig. 2 for representative tracing.) The indirect pressures were not recorded simultaneously but obtained from the records and, in many instances, several days elapsed between the two estimations

TABLE I. SUMMARY OF CLINICAL DATA

CASE	AGE	FEMORAL PULSES	X-RAY		ELECTRO-CARDIOGRAM	SUGGESTIVE MURMUR	SYMPTOMS
			HEART SIZE	RIB NOTCHING			
1	29	Diminished	Normal	+	Normal	+	None
2	23	Diminished	Normal	0	Normal	+	None
3	18	Good	Normal	0	Normal	+	None
4	20	Markedly diminished	Enlarged	+	Normal	+	Palpitation
5	21	Diminished	Enlarged	+	Normal	+	None
6	19	Feeble	Enlarged	+	L.V.H.	+	None

of the blood pressure. The electrocardiograms consisted of unipolar limb leads and 9 precordial leads: V_3R through V_8. All patients were fluoroscoped with barium swallow and x-ray studies were done with particular attention given to the posteroanterior and the left anterior oblique views. Anterior displacement of the esophagus caused by the poststenotic dilatation of the aorta was demonstrated in all cases, and was a most helpful finding. A typical murmur recorded from Case 4 is shown in Fig. 3.

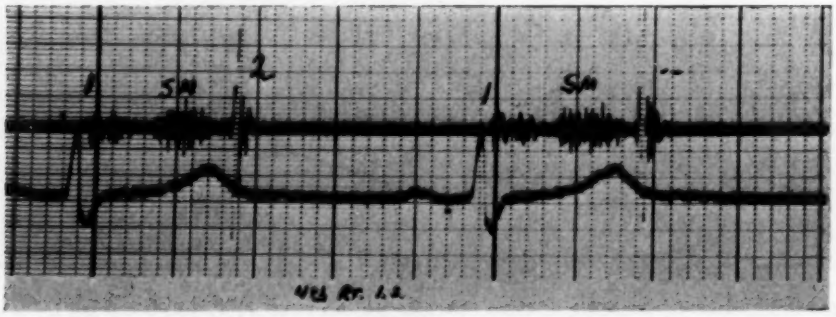

Fig. 3.—A typical systolic murmur recorded in the fourth right intercostal space, from Case 4.

RESULTS

The results are shown in Table II. In one case the direct intra-arterial pressure in the right brachial artery was 155/83 mm. Hg and in the other five cases the highest systolic pressure was 137 mm. Hg and the highest diastolic pressure was 88 mm. Hg. In six subjects considered to be normal, the range of the ratio of femoral to brachial pulse pressure was from 1.52 to 0.92. In our six cases of coarctation the range of the ratio of femoral to brachial pulse pressure was 0.76 to 0.28. This was the most consistent finding. The time of the onset of the femoral pulse was, on the average, delayed beyond normal values when compared with the time of onset of the brachial pulse, but in three instances did not exceed the range of the controls. In coarctation and controls there was also some over-

lapping of measurements of the time of occurrence of the peak of the femoral pulse as compared with the same point in the brachial artery tracings. However, the time elapsing from onset to the peak of the femoral pulse varied from 0.14 to 0.26 second in the coarctations, and in the normal controls from 0.11 to 0.14 second. These figures are in general agreement with the published results of Brown and associates,[5] when consideration is given to the fact that we have recorded brachial artery pulse tracings, and in their series radial arteries were used.

TABLE II

CASE	DIRECT ARTERIAL PRESSURES		RATIO FEMORAL TO BRACHIAL PULSE PRESSURE	FEMORAL DELAY		ONSET TO PEAK FEMORAL	INDIRECT CLINIC B.P.
	BRACHIAL	FEMORAL		ONSET	PEAK		
1	127/65	89/53	0.58	0.03	0.08	0.21	140/90
2	127/76	96/62	0.55	0.03	0.09	0.23	120/82
3	155/83	108/53	0.76	0.04	0.03	0.14	144/70
4	137/80	85/61	0.42	0.05	0.09	0.23	160/80
5	119/59	84/67	0.28	0.01	0.04	0.26	186/108
6	127/88	100/89	0.28	0.05	0.06	0.22	160/110
Average	132/75	94/64	0.48	0.04	0.06	0.21	151/90
Range of 6 normals		Greatest	1.52	0.03	0.07	0.14	
		Least	0.92	0.02	0.03	0.11	

COMMENT

None of these cases was treated surgically since the defect in our examinees existed prior to their entry into military service. We do not even suggest that these mild cases of coarctation should be treated surgically as the surgical risk must be balanced against the natural course of the disease, which is not as yet clearly defined. Surgical correction of mild coarctation would not alter the bicuspid aortic valve which is frequently associated. Many mild cases of coarctation of the aorta are probably not diagnosed even at autopsy,[6] and our opinion is that only those cases which are causing hypertension in the upper extremities, or left ventricular hypertrophy, should be operated upon. This opinion may change with the development of better surgical techniques.

We do suggest that coarctation of the aorta should not be excluded as a diagnosis simply because the blood pressure is normal and the femoral arteries can be palpated. The femoral artery pulsations must be evaluated in connection with the level of the blood pressure in the upper extremities, and when a typical murmur suggestive of coarctation is present x-ray studies of the chest, including a posteroanterior and a left anterior oblique view with barium in the esophagus, should be performed. In certain cases direct measurements of the arterial pressure can make the diagnosis which might be otherwise missed.

CONCLUSIONS

1. Coarctation of the aorta may exist with normal blood pressure in the upper extremities; six illustrative cases are reported.

2. When one finds a murmur at the level of the second to the fourth intercostal space beneath the sternum, and especially when this murmur is well heard in the back, coarctation of the aorta should be suspected despite the level of the brachial blood pressure by sphygmomanometry. This becomes especially pertinent if the femoral pulse, by palpation or measurement, are considered to be reduced (not absent).

3. The management of such mild cases of coarctation of the aorta should be individualized and surgery not necessarily recommended purely because the diagnosis is made.

4. In view of the fact that subacute bacterial endocarditis engrafted upon a bicuspid aortic valve, which is present in 42 per cent of the cases, is a potential hazard as well as bacterial endarteritis near the site of coarctation, the proper diagnosis becomes more important, even though the coarctation be mild and surgical treatment is not necessarily indicated. We believe that prophylactic antibiotics at the time of dental work and comparable surgical procedures are indicated to prevent bacterial endocarditis and endarteritis.

SUMMARIO IN INTERLINGUA

Sex juvene adultos mascule esseva studiate, principalmente a causa de murmures systolic, per medio de simultanee directe registrationes de pression arterial super un apparatura registratori del typo Hathaway. In omne casos le pression del arteria brachial esseva normal durante que le pression femoral esseva reducite.

Le characteristicas de leve coarctation del aorta es sublineate, e le importantia del diagnose de leve casos es discutite.

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A METHOD FOR THE SIMULTANEOUS DETERMINATION OF SYSTEMIC AND PULMONARY CIRCULATION TIMES

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THE purpose of this paper is to present a new clinical method for the simultaneous determination of the systemic and pulmonary circulation times. We shall not attempt to evaluate the significance and limitations of the circulation time tests, since they have been adequately described in the literature.[1-3]

There are as yet no methods, excluding catheterization, circulation time, and venous pressure studies, which yield definite information on the functional capacity of the heart, despite recent progress in electrocardiography, ballistocardiography, and vectorcardiography. Of the functional methods, catheterization is not without danger and requires in-hospital preparation. Both circulation time and venous pressure studies may be done as office procedures and are relatively free from danger. A correlation of circulation time and venous pressure determination is more accurate than either method used alone, and should be used in combination whenever possible. However, we are confining this paper to circulation time studies by the use of a new substance for this purpose, Intra-sul.*

Usually, as a routine work-up of the cardiac patient, the Decholin "arm-to-tongue" and the ether "arm-to-lung" circulation times are used. This involves the intravenous administration of two separate substances. The objections to this procedure are as follows:

1. Ether, when injected rapidly into the patient's vein, quite often causes pain and, at times, phlebitis.

2. It is not practical to use the ether test in the office, since no sterile commercial preparation in the small dosage form required in the test is available. A tin of ether has to be opened for each test and cannot be used again for further circulation-time tests.

3. When the injection of Decholin follows the injection of ether, it is sometimes noted that the arm-to-tongue time is longer than when the Decholin is injected first. (See Table I.)† This may be partially explained by the fact that

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*Intra-sul, which was supplied for this study by Crookes Laboratories, Inc., is a solution of sulfur in sodium sulfide and sodium thiosulfate. It has a pH of 9, and contains 20 mg. of sulfur per milliliter. It is essentially a stabilized solution of polysulfides, which produces a fine colloid of sulfur when injected. Shortly following its injection, intravenously, the patient is able to discern the characteristic odor of hydrogen sulfide ("rotten eggs") and a metallic, "brassy" taste, also characteristic of sulfides, which lasts for a few minutes.

†In this table it will be noted that in the few cases studied the "arm-to-tongue" time was always prolonged after the ether injection, and although this may be within the realm of experimental error, the findings were too consistent to be completely disregarded.

the previous rapid administration of ether causes a transient hemodynamic disturbance, possibly at the level of the lungs, so that when the Decholin is injected after the ether it has to flow through a vasoconstricted bed and takes a longer interval of time to reach the periphery. Apart from the physical factor, a psychologic one may also play a part, particularly when pain is associated with the preliminary ether injection.

TABLE I. SHOWING IN THE LAST COLUMN (F) THE DIFFERENCE IN SECONDS BETWEEN THE VALUES OF THE "ARM-TO-TONGUE" CIRCULATION TIME OBTAINED BY INJECTING DECHOLIN SOON BEFORE AND SOON AFTER THE ETHER

	CASE NO.	NAME	ARM-TO-LUNG IN SECONDS		ARM-TO-TONGUE IN SECONDS			DIFFERENCE BETWEEN THE VALUES OF COLUMNS C & D (SECONDS)
			ETHER	INTRA-SUL	DECHOLIN INJECTED		INTRA-SUL	
					AFTER ETHER	BEFORE ETHER		
Normal individuals	1	H.A.	7	6	16	14	14	2
	2	C.C.	6	4	16	15	15	1
	3	D.A.	8	8	18	14	15	4
	4	H.P.	8	6	18	16	16	2
Pathologic cases	5	B.K.	8	10	21	20	19	1
	6	R.K.	9	7	18	16	17	2
	7	E.L.	10	8	18	17	17	1
	8	K.B.	10	8	19	18	17	1
	9	M.O.	10	10	21	20	21	1
	10	J.T.	11	10	20	19	19	1
	11	N.F.	12	11	22	22	22	0
	12	H.McC.	12	11	24	21	21	3
	13	V.S.	12	13	23	23	21	0
	14	G.H.	13	12	22	20	20	2
	15	W.T.	14	12	24	23	22	1
	16	M.C.	15	16	27	26	25	1
			A	B	C	D	E	F

4. The comparison of results obtained from the injection of two unlike chemical substances, one for the "arm-to-lung" and the other for the "arm-to-tongue," may also be another source of error.

Our proposed method tends to obviate such limitations, since we are using a single substance for both tests and since both objective and subjective observations serve as a double check.

When the circulation time test was first introduced to the clinical study of the patient in 1922, Koch[4] injected fluorescein into a vein of the arm and timed the interval which elapsed before this substance was detected at the lips, by means of a Wood lamp. In so doing, he recorded the time of the flow from the vein to the right heart circuit, from there through the pulmonary arteries to the lungs, then through the pulmonary veins back to the left heart, and finally from there through the aorta and the arteries to the capillaries of the lips. It is

evident that such a method cannot give information sufficient to determine, in case of a deceleration, just where the delay is occurring. This may be in the veins, or through the lungs, or in the arterial segment, and the final result would be the same in all instances. For the same reason, the method of Blumgart and Weiss[5] of injecting radium C and detecting it by a Wilson Cloud Chamber in different parts of the body constituted no improvement, nor did the method of Spier, Wright, and Saylor.[6] The latter employed a combined solution of magnesium sulfate, calcium gluconate, sodium chloride, and copper sulfate, and recorded the circulation time from a vein to different levels of the arterial tree, according to the feeling of warmth the patient noticed successively in the tongue, perineum, hands, and feet. This method is very useful in particular cases, as when an arterial obstruction is suspected, or in cases of a vasculopathy.

In 1935, Hitzig[7] devised a method for differentiating the right from the left heart circuits. By injecting a small quantity of ether intravenously he obtained the "arm-to-lung" time. It was thus possible to get single evaluations of the blood speed in different sections of the vascular system. The ether method represents a valuable test, not only for differentiating the circulation time of the pulmonary tree from the systemic one, but also for detecting, indirectly, a congenital, or more rarely, an acquired venous-arterial shunt. Recently Ziegler[8] described a method for determining the circulation time from the right ventricle to the ocular and oral mucous membranes by injecting fluorescein into the ventricle during cardiac catheterization. This method, which gives the "right heart-to-face" circulation time, is useful in special cases. It has now become customary to perform the ether test, together with any other method to measure the "vein-to-artery" time interval, for the complete clinical study of the circulation.

METHOD

The method used by us has the advantage of employing a single, nontoxic substance for both the "arm-to-lung" and "arm-to-tongue" circulation times by means of one injection. In addition it is both subjective and objective in that the physician and the patient can both smell the hydrogen sulfide. The patient also detects a few seconds later a distinctive sharp metallic taste apart from the smell which abates in three to five minutes. Each one of these endpoints acts as a check on the other since acuity in taste and smell are freqently different in all of us.

The substance, Intra-sul, has been used intravenously for the past twenty-five years in the treatment of arthritis and has been found to be stable, nontoxic, painless, and on the whole, not objectionable. These circumstances made us consider the possibility of using the drug for the circulation time tests. We feel that this substance approaches the requirements delineated by Spier[6] and Hussey[9] for the ideal drug to be used for circulation time studies; namely, it is a safe drug, does not influence the conditions to be studied in the patient, does not upset the patient, and is promptly eliminated so that the test may be repeated, if necessary.

For the purposes of this investigation, the test was first performed on healthy normal persons as a control group, and then on known cardiac patients, using both the Intra-sul and the ether-Decholin circulation time methods for comparison and evaluation.

Three groups of patients were studied: One consisted of patients on the medical service of Misericordia Hospital; another of patients from the second medical service at City Hospital, Welfare Island; and the third group from cases in the Out-Patient Department of Misericordia and from private practice. In the latter group the test was performed in the clinic or in the office, and required no special preparation. Altogether we compiled data from over 200 patients. The results from the Misericordia group, Tables II and III, are representative of the total group.

TABLE II. NORMAL SUBJECTS

CASE NO.	NAME	AGE	SEX	CIRCULATION TIMES (IN SECONDS)				VENOUS PRESSURE IN Cm H_2O
				ARM-TO-LUNGS		ARM-TO-TONGUE		
				ETHER	INTRA-SUL	DECHOLIN	INTRA-SUL	
1	C.L.	8	F	4	5	9	10	–
2	G.J.	10	M	8	7	15	14	–
3	J.P.	28	M	8	7	16	14	7
4	C.C.*	29	M	6	4	15	15	8
5	G.C.	30	M	6	8	13	14	6
6	H.H.	31	M	6	7	13	14	–
7	D.A.*	36	F	8	8	18	15	9
8	R.W.	37	M	7	8	14	13	–
9	H.A.*	42	F	7	6	16	14	8
10	H.P.*	50	F	8	6	18	16	–
11	A.B.	52	M	7	7	14	13	8
12	P.S.	56	M	8	9	15	16	–
13	C.M.	57	F	5	6	11	13	–
14	S.C.	61	M	8	10	16	16	–
15	I.P.	64	F	8	9	16	17	9
Average				6.9	7.1	11.5	11.6	

*The same patients have been reported on Table I.

The test on hospitalized patients was usually performed in the morning, before breakfast. The patient was required to lie in bed quietly for at least thirty minutes prior to the test. He was instructed to indicate instantly when he could smell and taste the substance. For the standard tests, an antecubital vein was punctured with a 19-guage needle, the tourniquet released, and after thirty seconds, 5 minims of ether plus 10 minims of sterile water were rapidly injected. After the patient smelled the ether, 5 c.c. of 20 per cent Decholin were given through the same needle. Thirty to forty-five seconds later, through the same vein or another vein of the same arm, we injected the Intra-sul as rapidly as we had done the other two substances. It was sometimes necessary to change

the vein because of blood clotting. When the venous pressure was recorded, it followed the circulation time studies. At first this procedure was carried through with the three tests in order to obtain a comparison. Subsequently, the Intra-sul test was repeated alone on the same patient at a later date.

The amount of Intra-sul injected at the beginning of our work was 2 c.c., but after the first twelve cases, we increased the dose to 4 c.c. to sharpen the end-point. The times were recorded with a stop watch from the very beginning of the injection, which was administered very rapidily, the patient previously having been instructed to report the smell and taste instantly, and the physician also having been prepared to smell the characteristric odor from the patient's nose and mouth.

RESULTS AND DISCUSSION

A. *Normal Subjects.*—Table II gives the results of the tests performed on fifteen normal subjects: six females and nine males, whose ages ranged from 8 to 64 years.

As shown in the table, the values obtained by both the ether and Decholin tests, and the Intra-sul were almost identical. The mean values found for the "arm-to-lung" circulation time were 6.9 seconds with ether and 7.1 seconds with Intra-sul; and for the "arm-to-tongue" circulation time, 11.5 seconds with Decholin and 11.6 seconds with Intra-sul.

Although these figures cannot be taken as standard physiologic values because of the limited number of subjects and the great variation in their ages, they do show that the Intra-sul is as reliable a substance for the circulation time test as are ether and Decholin.

In the "arm-to-lung" time, the differences between the mean values given by the two methods was 0.2 second. In no single instance was the difference longer than 2 seconds.

In the "arm-to-tongue" time, the difference between the mean values was 0.1 second, while the greatest single difference was 3 seconds (Case 7).

B. *Pathologic Cases.*—Table III shows the values obtained in fifty-five patients suffering from different ailments, primarily cardiovascular.

The mean value for the "arm-to-lung" circulation time was 14 seconds with ether, and 12 seconds with Intra-sul; and for the "arm-to-tongue" circulation time was 21 seconds with Decholin and 20 seconds with Intra-sul.

The difference between the mean values was greater in this group than with the normal subjects. For the "arm-to-lung" circulation time it was 2 seconds and for the "arm-to-tongue" 1 second. In certain individuals we observed a greater difference in the times obtained with the two methods. This is illustrated by Case 3.

The difference observed in these cases may be explained by an instability in their cardiovascular status. However, the difference was usually small and did not greatly affect the clinical evaluation. A comparison could always be made between the two sets of values.

In one case (Case 38) the Intra-sul test failed; the patient did not smell or taste the substance at all, while he had previously been quite definite in detect-

TABLE III. PATHOLOGIC CASES

CASE NO.	NAME	AGE	SEX	CIRCULATION TIMES (IN SECONDS)				VENOUS PRESSURE IN Cm H_2O	DIAGNOSIS
				ARM-TO-LUNGS		ARM-TO-TONGUE			
				ETHER	INTRA-SUL	DECHO-LIN	INTRA-SUL		
1	M.O.*	24	M	10	10	21	21	14	Rheumatic heart disease—mitral stenosis and insufficiency; decompensated
2	S.d.C.	48	F	23	20	32	29	—	Rheumatic heart disease—mitral stenosis, aortic insufficiency, auricular fibrillation—congestive heart failure
3	R.P.	55	F	40	46	55	59	29	Arteriosclerosis—aortic insufficiency, auricular fibrillation—congestive heart failure, multiple myeloma
4	L.O'K.	48	M	24	25	31	30	19	Myocardial infarction—congestive heart failure
5	S.P.	42	F	11	10	17	16	—	Obese—arterial hypertension
6	J.T.*	45	M	11	10	20	19	15.5	Arteriosclerosis—myocardial infarction
7	K.B.*	42	F	10	8	19	17	12.5	Arteriosclerosis—auricular fibrillation
8	R.B.	53	M	12	14	18	19	10	Arteriosclerosis—cirrhosis of Laennec—ascites and edema
9	E.R.	10	M	10	10	14	13	—	Bronchial asthma—pulmonary emphysema
10	P.R.	72	M	12	14	20	23	—	Arteriosclerosis—mitral stenosis, aortic insufficiency—congestive heart failure
11	F.McD.	70	M	15	16	22	22	—	Arteriosclerosis—coronary insufficiency—auricular fibrillation—hypertension
12	G.S.	73	M	8	9	15	15	—	Arteriosclerosis—bronchopneumonia bilateral
13	J.R.	77	M	10	10	?	17	—	Arteriosclerosis—carcinoma of the lungs
14	H.McC.*	34	F	12	11	24	21	19	Rheumatic heart disease—mitral stenosis—pulmonary edema
15	M.G.	72	M	13	11	19	18	—	Arteriosclerosis—left bundle branch block—pyelonephritis—edema
16	M.P.	61	M	9	10	16	16	—	Arteriosclerosis—diabetic gangrene
17	B.K.*	67	M	8	10	21	19	17.5	Chronic cor pulmonale—pulmonary emphysema
18	F.T.	55	M	9	8	15	13	—	Arteriosclerosis—coronary insufficiency
19	J.L.	42	M	12	13	16	18	13	Diabetes—chronic nephritis—hypertension—edema
20	E.L.*	71	F	10	8	18	17	—	Arteriosclerosis—mitral stenosis
21	B.R.	59	F	10	12	14	15	8	Arteriosclerosis—hypertension
22	A.V.	14	M	7	8	12	12	—	Rheumatic heart disease—serofibrinous pleurisy
23	E.S.	31	M	9	8	15	14	8	Rheumatic heart disease—congestive heart failure
24	N.F.*	54	M	12	11	22	22	16.5	Arteriosclerosis—auricular fibrillation, mitral insufficiency and stenosis

25	W.T.*	37	F	14	12	24	22	—	Scoliosis—chronic cor pulmonale—pulmonary edema
26	L.B.	42	F	13	12	19	19	—	Diabetes—myocardial infarction
27	F.P.	62	M	10	11	18	20	—	Silicosis—chronic cor pulmonale
28	G.H.*	64	M	13	12	22	20	16.5	Arteriosclerosis—hypertension
29	C.D.	45	M	13	12	21	20	—	Emphysema—chronic cor pulmonale
30	M.F.	57	M	11	12	18	18	—	Chronic alcoholism—possible liver involvement
31	A.B.	76	M	20	22	28	28	—	Arteriosclerosis—myocardial infarction
32	V.S.*	34	F	12	13	23	21	14	Rheumatic heart disease—mitral stenosis—congestive heart failure
33	M.C.*	28	F	15	16	27	25	—	Rheumatic heart disease—auricular fibrillation—congestive heart failure
34	W.F.	69	M	11	12	17	18	11	Arteriosclerosis—coronary insufficiency
35	F.D.A.	61	F	9	8	14	14	10	Diabetes—arteriosclerosis—hypertension—carcinoma of the stomach
36	F.C.	54	M	28	26	36	34	21.5	Second degree burns—50% body surface—ventricular tachycardia
37	R.K.*	45	F	9	7	18	17	—	Arthritis—Parkinson's disease
38	M.McS.	66	M	10	?	18	?	10	Bronchial asthma—hypertension—congestive heart failure
39	F.S.	52	F	20	22	27	28	19	Diffuse carcinomatosis from cancer of breast
40	T.C.	48	F	16	15	23	23	14	Pulmonary emphysema—auricular fibrillation—coronary insufficiency—congestive heart failure
41	V.T.	55	M	15	16	23	23	—	Arteriosclerosis—left bundle branch block—pulmonary edema
42	E.W.	52	F	18	17	25	?	—	Hypertension—arteriosclerosis
43	A.H.	56	F	17	16	23	23	—	Arteriosclerosis—myocardial infarction—A-V block
44	B.M.	62	F	15	14	20	21	—	Rheumatic heart disease—mitral stenosis and insufficiency—auricular fibrillation—congestive heart failure
45	R.S.	25	F	18	20	25	28	18	Obese—hypertension
46	E.D.	56	F	12	13	18	18	—	Bronchial asthma—emphysema—chronic cor pulmonale—congestive heart failure
47	T.F.	51	M	18	17	26	24	16	Arteriosclerosis—hypertension
48	T.C.	56	M	12	13	17	17	15	Arteriosclerosis—hypertension
49	A.C.	21	F	10	11	15	15	9.5	Rheumatic heart disease—mitral insufficiency and stenosis
50	P.F.	70	M	10	9	16	14	10	Arteriosclerosis—myocardial fibrosis
51	A.H.	67	F	16	17	22	22	19	Arteriosclerosis—auricular fibrillation—congestive heart failure
52	A.O'B.	59	F	10	11	18	19	10	Lobar pneumonia
53	A.D.	65	F	20	21	26	26	15	Arteriosclerosis—hypertension
54	C.B.	66	F	16	18	26	28	14.5	Arteriosclerosis—auricular fibrillation
55	S.B.	45	F	36	34	46	42	18	Coronary insufficiency—edema
	Average:			14	12	21	20		

*The same patients have been reported on Table I.

ing both the ether and the Decholin. The test was repeated in half an hour and again the next day but the patient still could not detect the end point. Usually the characteristic smell of the Intra-sul was noticed not only by the patient but also by the observer, and the objective finding was practically simultaneous to the subjective one in most instances. In the case under discussion (Case 38), the observer as well as the patient failed to detect the smell of the substance. We are not able to explain satisfactorily such a peculiarity and we can only point out that in some cases the end point may also not be reached with ether and Decholin. Also the senses of taste and smell may be defective or absent in any individual. Case 13 is an example of this; the patient could not taste the Decholin in any of three consecutive tests.

SUMMARY

A method for the determination of the circulation time, using a solution of sulfur (Intra-sul) as the testing substance, is reported. The main advantage of this method is that both "arm-to-lung" and "arm-to-tongue" circulation times may be estimated by a single intravenous injection. It is noteworthy that this method allows subjective and objective observation of the "arm-to-lung" time.

The method has been used on over 200 patients without any serious side reactions, and with a minimum of discomfort to the patient.

The results of the Intra-sul test on fifteen normal individuals and on fifty-five patients with various illnesses are reported, together with a comparison of ether and Decholin with the Intra-sul tests. The findings show that the results with Intra-sul are comparable with those obtained with ether and Decholin.

The test is relatively simple and can be performed as part of an office procedure.

SUMMARIO IN INTERLINGUA

Es reportate un nove methodo pro le determination del tempore circulatori. Le substantia testatori usate esseva Intra-sul, i.e. un solution de sulfure in sulfido e thiosulfato de natrium. Le principal avantage del methodo es que le duo tempores circulatori "ab bracio a pulmone" e "ab bracio a lingua" pote esser estimate con un sol injection intravenose. Il es notabile que iste methodo permitte le subjective e le objective observation del tempore "ab bracio a pulmone."

Le methodo esseva usate in plus que 200 patientes sin serie reactiones lateral e con un minimo de discongorto pro le patiente.

Es reportate le resultatos de tests a Intra-sul in 15 individuos normal e in 55 patientes con varie morbos, insimul con un comparation con tests a ethere e Decholina. Le constatationes obtenite indica que le test a Intra-sul es comparabile in su resultatos con le tests a ethere e Decholina.

Le test es relativemente simple e pote esser executate como parte del routine del sala de consulta.

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ERRORS IN EVALUATION OF THE SEVERITY OF HYPERTENSION

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FOR a long time it has been known that a great many drugs and procedures will affect arterial hypertension favorably in so far as the level of blood pressure is concerned. In fact, any therapeutic procedure vigorously pursued by both physician and patient may cause a change in numerical values as measured by the physician.[1] Furthermore, Ayman was probably the first to show that "casual" readings made under the tension of a visit to a physician's office might be erroneously high,[2] although Janeway, in 1904, was well aware of the hypertensive effect of emotion.[3] In a previous study we have drawn attention to the moment-to-moment variations in blood pressure, dependent upon respiratory and Traube-Hering waves, which may be as great as 20 to 30 mm. Hg systolic,[4] also known for over 50 years.[3] The present report concerns a group of patients, all of whom might have responded well to any new or old therapeutic regimen, provided adequate cooperation between patient and physician had been achieved. Its purpose is to point out the necessity of carefully screening individuals to whom potent antihypertensive drugs are to be given in order to be sure that sustained hypertension is actually present.

MATERIAL AND METHODS

Patients were selected only in that they were referred to us by other physicians for control of what was believed to be severe and sustained hypertension of considerable duration. On first consultation the blood pressure was measured during the physical examination. A decision was then made as to whether or not the patient should enter the hospital for initiation of control of hypertension by ganglionic blocking agents and hydralazine.[5] In our opinion, induction of control by these agents necessitates initiation in hospital in order to avoid hypotension and obstipation, the two important serious side effects. So as to evaluate the effectiveness of the newer and potent chemotherapeutic agents in severe forms of hypertension, a concerted attempt was made to exclude milder cases which might respond favorably to reserpine or a combination of reserpine and hydralazine given on an outpatient basis. The individuals here discussed were considered suitable candidates for hospitalization and the use of ganglionic block-

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ing agents, inasmuch as prior levels of blood pressure, symptoms, and physical findings suggested to two or more independent observers that control might be necessary for prolongation of life or prevention of disability.

In fifteen cases among 247 admissions to hospital an error in judgment was made in that the hypertension was considered by the referring physician and by us to be severe and sustained enough to warrant the use of ganglionic blocking agents. Each patient was examined by an assistant resident physician and an intern. Orders were left that the blood pressure be measured by nurses every four hours, day and night, and charted; this routine included both resting (or "basal") values and those attained during normal activity. Patients were not

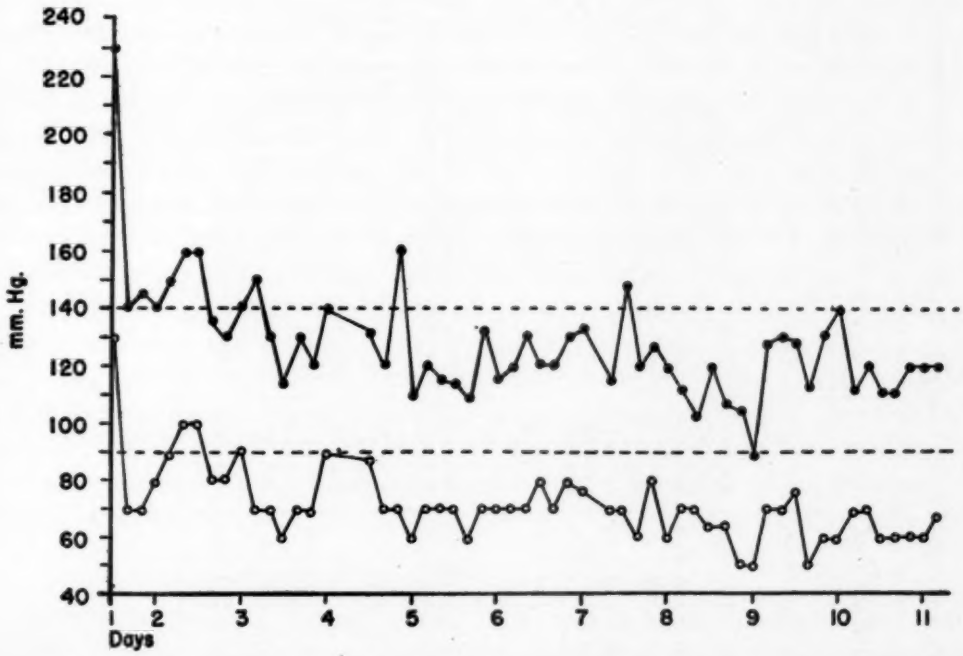

Fig. 1.—Typical rapid fall of blood pressure after hospitalization. E. E. was a 39-year-old woman who was first discovered to have an elevated blood pressure six years previously at the time of pregnancy, complicated by pyelonephritis. During the intervening years her blood pressure was always elevated in a physician's office. Six months and one month prior to admission she suffered two attacks of severe headaches, numbness and weakness of one side of her body, and loss of consciousness for one to three hours, with gradual recovery during the following week. Her blood pressure was said to have varied between 230/130 and 210/110 mm. Hg for two years. She complained of dyspnea on exertion and dizziness. On examination there was one small retinal hemorrhage. Blood pressure was 238/136. Her heart was enlarged to the left in x-ray photographs. Renal function was excellent. No cause for the attacks was discovered on careful neurologic examination. The first pressure shown (230/130 mm. Hg) was measured by both the intern and assistant resident the night of admission; subsequent ones were measured by nurses beginning the following morning.

confined to bed. All were subjected to various diagnostic procedures often new to them, such as electrocardiography, intravenous pyelography, studies of renal function, and the injection of drugs for specific tests. Although all were handled similarly, different nurses and members of the house staff attended them. An attempt was made to avoid psychotherapeutic influences in so far as possible.

TABLE I. FALL OF BLOOD PRESSURE IN HOSPITAL WHEN MEASURED BY NURSES (MM. HG)

PATIENT	AGE (YR.)	SEX	STATED DURATION OF DISEASE (YR.)	PHYSICIAN'S READINGS			NURSES' READINGS			TIME TO FALL TO NORMAL (DAYS)	ABNORMAL FINDING*	REMARKS
				RANGE	OUTSIDE	ADMISSION	FIRST	LOWEST	LAST			
R. Fr.	52	♀	13	230/110	200/90	200/90	200/90	120/75	160/94	4		Obesity
	56					230/98	204/100	140/80	145/90	6	Ht.	Obesity
E. Ek.	39	♀	6	230/130	210/110	230/130	140/70	90/50	120/66	1	E., Ce.	Emotional instability
E. Si.	37	♀	18	180/	250/	194/114	170/120	130/80	150/95	2	Ht.	Emotional instability
	37+					190/120	172/120	130/70	160/100	2		
R. Sh.	54	♂	1½	180/120	170/110	170/110	162/98	130/70	134/90	1	Ht.	Atherosclerosis
A. Ha.	54	♀	9	170/110	135/90	165/88	130/80	135/80	138/90	1		Emotional instability
	58			180/120	160/90	155/90	170/94	134/84	136/90	2	Kid.	
E. Cl.	56	♀	10	225/120	200/118	190/118	150/90	100/70	100/70	1	O	Obesity
L. Ch.	25	♂	13	230/	180/	176/120	180/110	120/80	160/95	1	Ce.	Emotional tension
M. He.	54	♀	10	220/	200/	178/100	142/90	120/70	120/64	1	Ht.	Obesity
E. Ba.	42	♀	2	240/140	220/120	195/105	170/110	110/70	102/60	1	Ht.	Obesity
J. Ho.	29	♂	12	220/	180/	180/110	170/110	130/80	138/90	2	Ht.	Emotional tension
O. Br.	48	♀	6	230/	180/	218/112	130/80	110/66	140/100	1	Ht. Kid.	Obesity
W. McI.	66	♂	3	225/	200/	220/100	204/100	130/80	180/100	3	Ht.	Atherosclerosis
	67					220/120 210/95	170/100	130/70	175/95	5	Ht.	
F. Le.	44	♂	½	200/	160/110	180/110	160/110	120/80	140/110	2	Ht.	Emotional instability
M. Pe.	53	♀	11	200/	180/	214/120	220/120	140/90	140/80	4	Ht.	Obesity
M. Br.	72	♀	15	210/110	180/90	165/95	170/85	110/75	120/60	1	Ht.	Atherosclerosis
Mean	49.6		8.67	215/120	183/103	194/107	169/99	123/74	140/87	2.2		

*Ht. = cardiac enlargement by x-ray and/or ECG.
Kid. = reduced renal function by test of excretion of phenol red.
E. = hemorrhage or exudate in retina.
Ce. = cerebral symptoms.

Sedatives were not employed, except during a sodium amytal release test given to the four whose blood pressures were elevated after two days in the hospital. The range of blood pressure found by referring physicians in their offices, the levels found on admission to the hospital by resident physicians, and those measured by nurses every four hours were then compared.

RESULTS

Table I shows the ranges of blood pressure obtained by physicians compared with the values obtained by nurses. In all of these cases marked falls to normotensive levels occurred under the routine of the hospital. In nine, the level of blood pressure became normal overnight (Fig. 1). In the remainder, a more gradual decline was observed with normal levels (140 mm. Hg systolic and 90 mm. diastolic) attained in two to six days. The mean decline from admission (physician's) to lowest (nurse's) levels was 71 mm. systolic and 31 mm. diastolic; the diastolic range was 16 to 80 mm. Seven subsequently exhibited mildly hypertensive levels before discharge. Therefore in no case could ganglionic blocking agents be used. Five of these patients, a year or more later, have required hydralazine and reserpine for control of blood pressure at normal or near normal levels while the remainder are taking reserpine alone.

Twenty-five comparable patients who were considered to exhibit less severe hypertension and therefore not to require hospitalization were examined in alphabetical order. All have been treated with reserpine alone; in only three has the blood pressure remained at strictly normotensive levels on each of several infrequent subsequent examinations. In the remainder, small daily doses of hydralazine have been required to produce lower levels of blood pressure, as recorded by physicians.

COMMENT

It appears probable that if these patients had become accustomed to having their blood pressures measured frequently, significant results would have been produced by any drug or procedure. In fact, results in some cases would have been dramatic, with reduction in systolic pressures of 80 to 100 mm. Hg and diastolic of 30 to 60 mm. overnight. That nothing was done except an evaluation in the hospital suggests that numbers of individuals in this country exhibit hypertension when blood pressure is measured by a physician and may not during the remainder of the time. As Ayman has shown,[2] it is possible that in some people the blood pressure becomes elevated only under stress and may appear so for years. In these the reassuring effect of medication or regimen might cause significant changes in a downward direction.

The value of the newer agents for the control of hypertension is well established.[5] Malignant hypertension is no longer the serious and fatal disease that it has been in the past.[6] Severe forms of benign hypertension (which do not respond to hospitalization and the measurement of blood pressure by nurses) can be controlled and slow reversal of secondary pathologic changes have been observed. It is essential, however, that a screening process be instituted to

select patients who have sustained hypertension all of the time for the evaluation of potent drugs and not to include those who appear to have it on the surface. The patients reported here were selected as carefully as possible, and every effort was made to avoid needless hospitalization. Eight came to us from considerable distances at some expense. All had been under the care of other physicians, often for several years. Yet, in spite of precautions, 6.1 per cent were erroneously considered to be in need of intensive therapy. Undoubtedly intermittent and severe hypotension would have resulted from the use of blocking agents.

These observations also emphasize the fact that any single reading of blood pressure is at the very best an approximation subject to interpretation by various other more stringent diagnostic measures. When falls of diastolic pressure of 20 to 40 mm. Hg occur as the result of a person other than a physician measuring it, the vascular lability exhibited by some individuals becomes obvious, as Smithwick has often observed.[7] Rigid criteria in the selection of patients is essential for evaluation of therapeutic procedures.

If the blood pressure of these patients had been measured daily rather than every four hours the changes might not have been as great. Before the four-hour schedule was instituted, our impression is that marked depressions were found more uncommonly. There may be such a thing as a "manometric reflex" in patients sensitized to the existence of their own hypertension.[8] When the cuff is wrapped about the arm, intense neurogenic vasospasm may occur before the examiner has time to inflate it. Furthermore, the act of compression of the cuff may raise blood pressure.[3] In such an event a false hypertension would be exhibited and mislead the physician in his evaluation of the patient for treatment; repetitive measurements by nonprofessional persons might in part negate this reaction.

SUMMARY AND CONCLUSIONS

Two hundred and forty-seven patients were referred by their own physicians for admission to hospital in order that severe, sustained, and prolonged hypertension be controlled by hydralazine and ganglionic blocking agents. From history and physical examination all of these were considered suitable candidates for admission. Fifteen developed sustained normotension when blood pressure was measured by nurses every four hours and no hypertension remained to be controlled. A screening procedure is essential in evaluation of potent antihypertensive drugs in order that such labile cases be excluded.

SUMMARIO IN INTERLINGUA

Le observationes del presente reporto se basa super un serie de 247 patientes que lor medicos private habeva referite al hospital pro le tractamento de sever, continue, e prolongate hypertension per medio de hydralazina e agentes ganglio-blocante. Le historia e le examine physic qualificave omne iste patientes como candidatos pro le admission al hospital. Quando le pression sanguinee esseva mesurate per le infirmeras del hospital a intervallos de quatro horas, 15 del subjectos disveloppava un stato durative de normotension e nulle hypertension remaneva pro le attacco therapeutic. In le evalutation de potente drogas anti-

hypertensive, le institution de un methodo de secernage es indispensabile a fin que tal casos labile pote esser excludite.

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Critique

AN ONTOGENETIC THEORY FOR THE EXPLANATION OF CONGENITAL MALFORMATIONS INVOLVING THE TRUNCUS AND CONUS

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IT IS our belief that most present theories explaining congenital truncoconal malformations are not always supported by consistent embryological or phylogenetic data.[8,9,11,12] This paper offers a new ontogenetic theory based upon Davis,[2,3] Streeter,[13] and Kramer's[7] modern school of human embryology, as well as on the study of pathologic specimens of patients dying with congenital heart disease, from the Instituto Nacional de Cardiología of México, and from the medical literature. Furthermore, one of us (M.V.C.) has had the opportunity of studying the material extant at the Department of Embryology of the Carnegie Institution of Washington which also served the afore-mentioned authors for their investigations.

NORMAL DEVELOPMENT OF THE TRUNCUS AND CONUS IN THE HUMAN HEART

Knowledge of the development of the truncus and conus in the human embryo requires a tenacious study of the heart at graded stages of embryonic development. We started our work by going over the series of embryos that Davis examined for his publication on the development of the human heart, from its first appearance to the stage found in embryos of twenty paired somites. We found, as Davis did, that in one of the earliest embryos (embryo No. 3709, Carnegie Collection) the heart consists of a bilaterally symmetrical myoepicardial mantle enclosing the bilateral and symmetrical endocardial plexus. This myoepicardial mantle forms two ventral folds; its dorsal borders have not yet been fused to that of the ventral wall of the pharynx, constituting the dorsal wall of the cardiac cavity.

While admittedly this article is extremely technical and may appeal to few of our readers, its originality is provocative and it merits publication.—Ed.

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At this stage of development, the myoepicardial mantle is, in itself, a canal and not a tube. Although the heart is extremely rudimentary, one can identify the following areas: aortic bulb, bulbus cordis or conus, ventricle, and atria. These zones are separated by the right and left interbulbar sulci, the right and left bulboventricular sulci, and the right and left atrioventricular sulci, respectively (Fig. 1, *A*,*B*). Following the study of the formation of the dorsal wall of the cardiac tube, we find that in the embryo No. 4216 of the Carnegie Collections, as described by Davis, the dorsal borders of the myoepicardial mantle have fused in the midline, at the level of the bulboventricular sulci. In more advanced stages of development, it is seen that from this dorsal point of fusion, the borders of the myoepicardial mantle continue fusing each other, cephalad, until reaching the interbulbar sulci, and caudad until the atrioventricular sulci. This is completed in embryo No. 4439 of Carnegie Collection. In the same embryo we can identify: a ventricle, a bulbus cordis (conus) of tubular form with well-formed

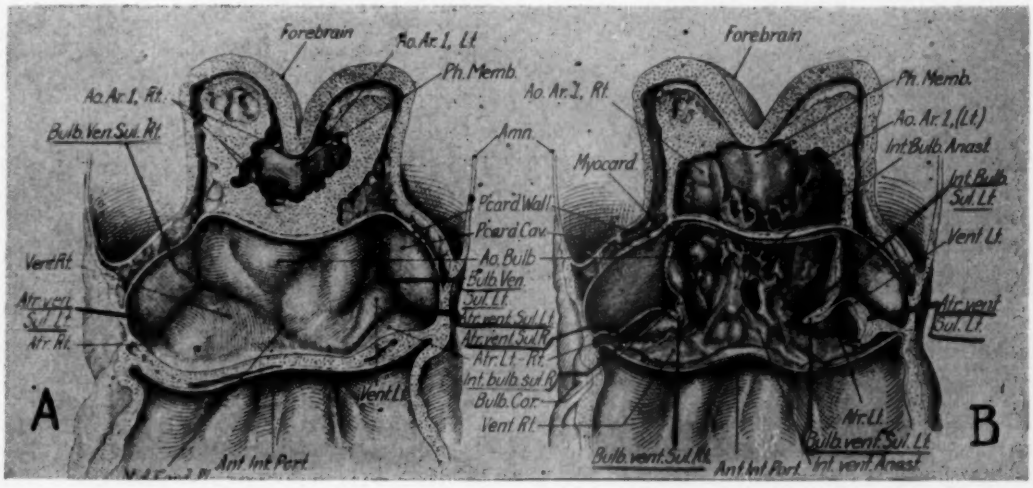

Fig. 1.—Ventral view of a plaster model of the heart and pericardial region (embryo 3709, Carnegie Collection). *A*, The ventral pericardial wall is removed to expose the myocardium. (×100.) *B*, The ventral myocardial wall has been dissected to expose the endocardium. (×100.) (From Davis, Contrib. Embryol., vol. 19, 1927.)

***Key to Abbreviations* (*Figs 1 and 2*)**

Amn.: Amnion
Ant. Int. Port.: Anterior intestinal portal
Ann'l. Cr. Lt., Rt.: Annular crest, left, right
Ao. Ar. 1, Lt., Rt.: First aortic arch, left, right
Ao. Bulb.: Aortic bulb
Atr. Lt., Rt.: Atrium, left, right
Atr. ven. Sul. Lt., Rt.: Atriovenous sulcus, left, right
Atr. vent. Sul. Lt., Rt.: Atrioventricular sulcus, left, right
Bulb. Cor.: Bulbus cordis
Bulb. Ven. Sul. Lt., Rt.: Bulbovenous sulcus, left, right
Bulb. vent. Sul. Lt., Rt.: Bulboventricular sulcus, left, right
Ent.: Entoderm
Int. Bulb. Anast.: Interbulbar anastomosis
Int. Bulb. Sul. Lt., Rt.: Interbulbar sulcus, left, right
Int. vent. Anast.: Interventricular anastomosis
Mand. Bar. Lt., Rt.: Mandibular bar, left, right
Mid. Card. Pl.: Middle cardiac plate
Myocard.: Myocardium
Myoend. Sp.: Myoendocardial space
P'card. Cav.: Pericardial cavity
P'card. Wall: Pericardial wall
Ph. Memb.: Pharyngeal membrane
Sept. Trans.: Septum transversum
Sin. Ven.: Sinus venosus
Umb. V. Lt., Rt.: Umbilical vein, left, right
Vent. Lt., Rt.: Ventricle, left, right
Vit. V. Lt., Rt.: Vitelline vein, left, right

walls (except for the aortic bulb and atria which, at this stage, are still open dorsally). By the time the bulbus cordis (conus) acquires its dorsal wall, the interbulbar sulci, which separated it from the aortic bulb, and the bulboventricular sulci, which separated the bulbus cordis from the ventricle, continue developing in a different manner.

For a clear understanding of the progressive changes which take place at the boundaries of the bulbus cordis (with the aortic bulb and with the ventricle, respectively), it is necessary to focus our study upon the graded changes of the sulci (interbulbar and bulboventricular) inasmuch as these sulci are, in fact, the limits of the bulbus cordis.

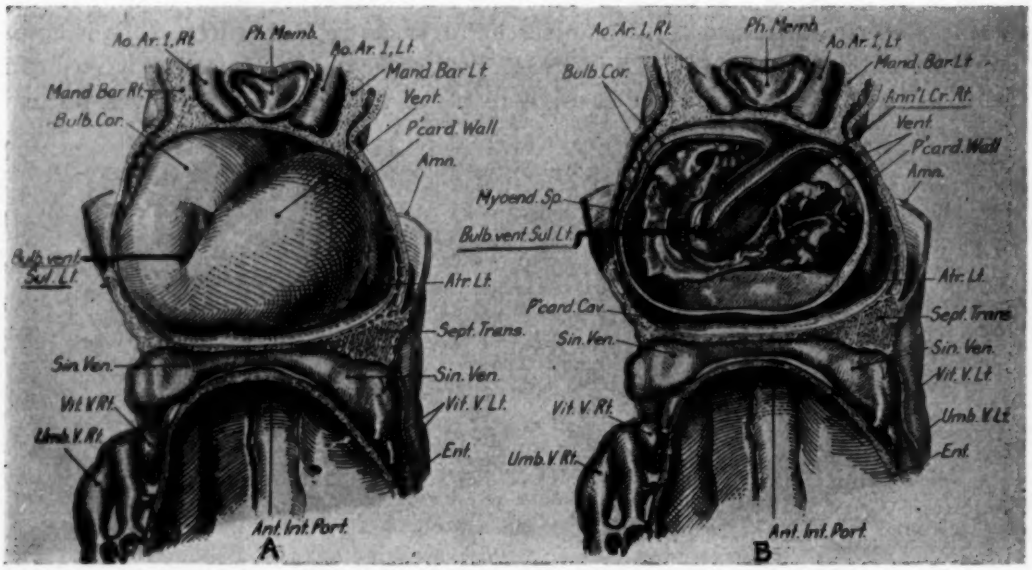

Fig. 2.—Ventral view of plaster model of heart and pericardial region (embryo 4529, Carnegie Collection). *A*, Pericardial wall removed to expose myocardium. *B*, Ventral myocardial wall also dissected to expose endocardium. (×100.) (From Davis, Contrib. Embryol., vol. 19, 1927.) ***For key to abbreviations, see p. 783.***

Thus we find that the interbulbar sulci become less and less deep until they vanish, as seen in embryo No. 3707 of the Carnegie Collection, the limit line between the bulbus cordis (conus) and the aortic bulb has then disappeared. The right bulboventricular sulcus has at this time almost disappeared, while the left bulboventricular sulcus becomes deeper and forms a narrow slit between the proximal bulbus cordis (conus) and aortic bulb on one side, and the distal ventricle at the other side. In this same embryo the bulboventricular loop has also been formed.

In the older embryos of Davis' series, ranging from eleven to twenty paired somites (No. 4529, 470, and 2053 of the Carnegie Collection) in which the bulboventricular loop forms an arc of about 180 degrees, the right bulboventricular sulcus has entirely disappeared. The bulboventricular loop has two limbs: one is formed by the bulbus cordis and the other by the ventricle. The bulbar limb (bulbus cordis or conus) continues cephalad, without lines of demarcation, with the aortic bulb, and caudad with the other limb, i.e., the ventricle. The

left bulboventricular sulcus at this stage constitutes, entally, a thick ridge forming the proximal and dorsal margins of the bulboventricular juncture or isthmus (Fig. 2, *A*,*B*).

On the endocardium of embryo No. 4529 of the Carnegie Collection, Davis described two shieldlike convex formations at the ventral aspect of the endocardium of the bulboventricular loop. One of these plates is located in the bulbar limb (bulbus cordis or conus) and the other, the most developed, in the ventricular limb of the bulboventricular loop. Following the evolution of the endocardial plates through embryos 470 and 2053, Davis found that the irregularities in these plates were transformed into endothelial trabeculae.

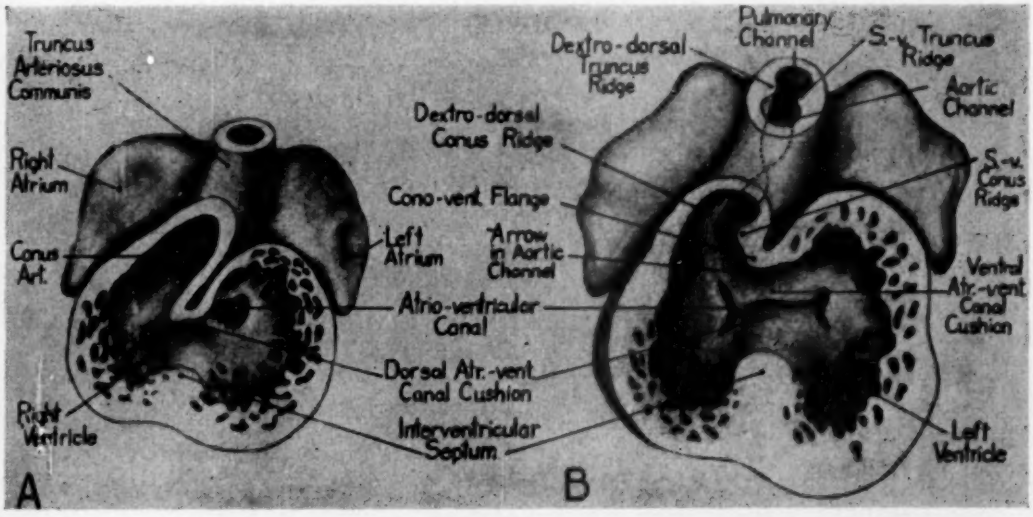

Fig. 3.—Semischematic drawings to show the early relations of the conus and the ventricle, and early stages in the partitioning of the truncus and conus, leading toward the establishment of the aortic and pulmonary outlets. *A*, Heart of an embryo about 4 to 5 mm. *B*, From a reconstruction of the heart of an 8.8 mm. embryo. (S. – v. = sinistroventral.) (From original of Fig. 6 A-B, Theodore C. Kramer, Am. J. Anat. 71:359, 1942.)

In the same manner as the bulbus cordis (conus) continues with the aortic bulb, as observed in embryo No. 3707 of Carnegie Collection, in the embryos studied by Kramer, which are older than those of Davis, the conus* continues in a cephalic direction and without a line of demarcation, with a structure named truncus arteriosus. Based on these facts, Kramer established an arbitrary boundary between the conus and the truncus arteriosus: the level at which the aortic and pulmonary valves are formed.

Once we have identified the bulbus cordis of Davis with the conus of Kramer, it is easy to conclude that the ental ridge of the left bulboventricular sulcus of Davis is identical to the conoventricular flange of Kramer, which is the last remnant of the boundary between the conus (bulbus cordis) and the ventricle (Fig. 3, *A*,*B*).

***When Kramer began his studies on the partitioning of the truncus and conus, he discussed the terminology used by foregoing embryologists. In order to avoid confusion with the terms utilized in comparative embryology, he decided to use the word "conus" instead of "bulbus cordis" or "bulbus conus arteriosus."**

Several years later Streeter, on studying the origin and evolution of the ventricular trabeculation, again used the Davis embryo, No. 2053, as well as a series of progressively older embryos, and was able to identify the origin of the ventricles (Fig. 4). He then found that the endocardial plates described by

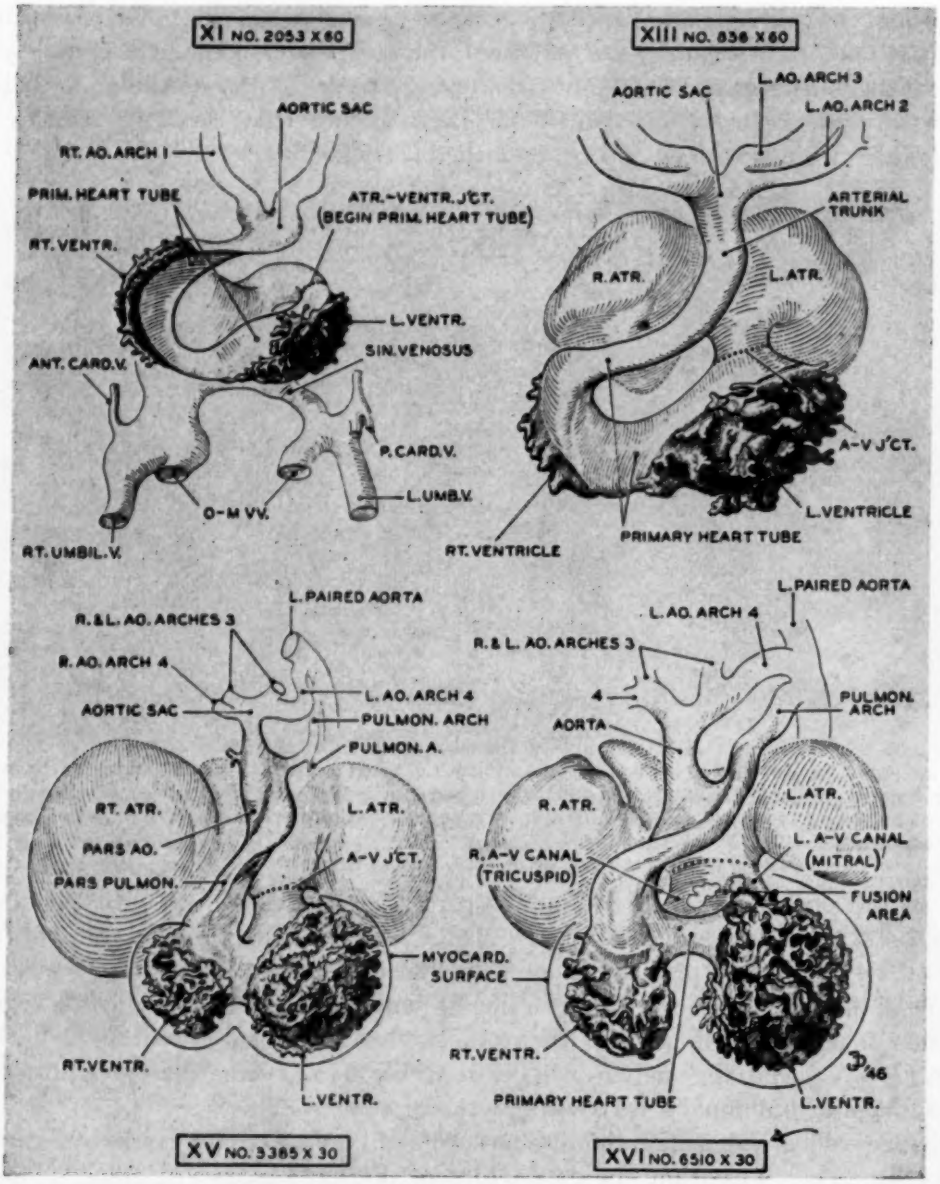

Fig. 4.—Drawings of plaster models (casts of cardiac cavities) to show the development of the ventricles. (From Streeter, Contrib. Embryol., vol. 32, 1948.)

Davis originate the trabecular zones of the ventricles: the plate located in the conus (bulbus cordis) gives rise to the trabecular portion of the right ventricle, while the endocardial plate located in the primitive ventricle is the origin of the

trabecular portion of the left ventricle. On the other hand, Kramer referred the origin of the cephalic portion of the outflow tract of both ventricles to the region of the conus close to the truncus arteriosus. In later stages of development, resorption and differential growth are determinant factors for the reduction of the conoventricular flange, making the conus shift from the extreme right toward the midline and its septum, coming into alignment with the muscular portion of the interventricular septum (Fig. 3, *A*,*B*). The union of the conal septum with the muscular interventricular septum is parasagittal. Thus the right border of the muscular interventricular septum will coalesce with the conal portion of the truncoconal septum. This explains why one of the great vessels emerges from the right and the other from the left ventricle (Fig. 5).

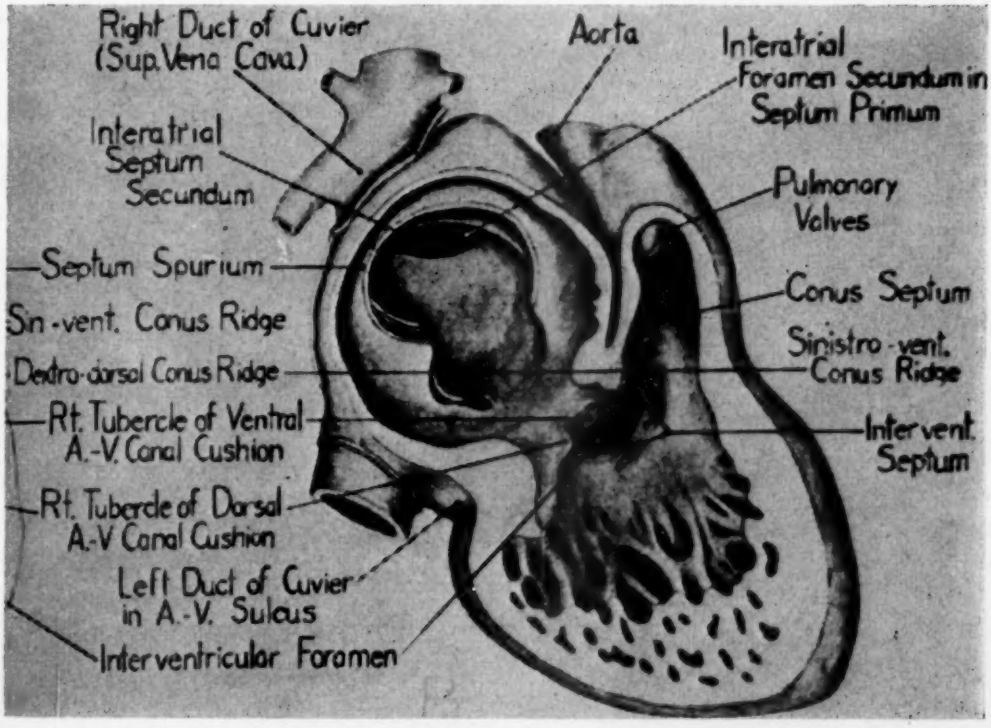

Fig. 5.—Semischematic representation of different components of the septal system in lateral aspect. Based on reconstructions of hearts of embryos 12 to 14 mm. (From original of Fig. 8 B, Theodore C. Kramer, Am. J. Anat. 71:363, 1942.)

By the time the conus shifts toward the midline and the conoventricular flange is disappearing, two longitudinal ridges are formed by concentrations of endocardial cushion tissue. From the beginning of its formation these longitudinal ridges extend, in a clockwise spiral path of about 180 degrees, from the cephalic end of the truncus arteriosus, through the conus, to the ventricle. These are called the truncoconal ridges.

Embryo E. H., No. 35 of the University of Michigan Collections, shows that the development of the two truncoconal ridges is not of the same degree at all levels. Three zones are the best developed: (a) in the ventral roots of the

aorta at the level where the fourth and sixth arches are being separated; (b) in the truncus arteriosus at the level where the pulmonary and aortic valves are destined to be formed; (c) in the conus, on the ventricular side of the location at which the sigmoid valves will appear.

Upon examination of each ridge separately, it is found that the spiral of approximately 180 degrees is formed in the following manner: the dextrodorsal truncus ridge continues with the sinistroventral conus ridge, and the sinistroventral truncus ridge with the dextrodorsal conus ridge (Fig. 3,*B*).

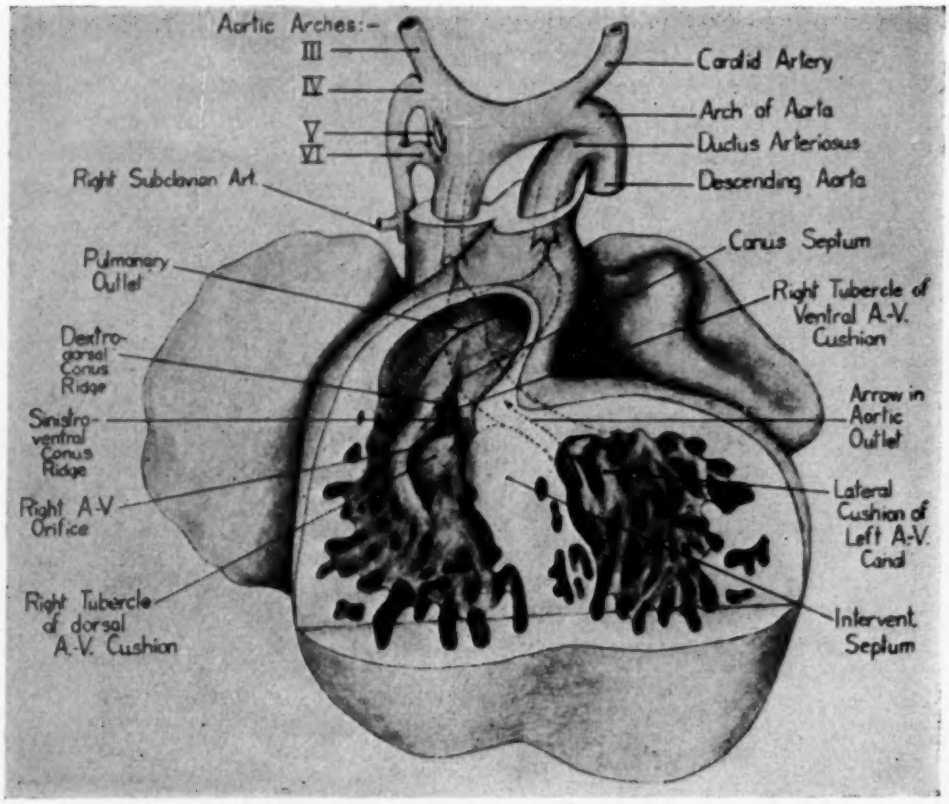

Fig. 6.—Ventral aspect of a reconstruction of the heart of a 13 mm. embryo (the ventral wall has been removed), to show the relations of the conus and the interventricular septa, as well as the great vessels. (From original of Fig. 9, Theodore C. Kramer, Am. J. Anat. 71:365, 1942.)

The two truncoconal ridges grow toward the lumen of the truncus-conus, become fused, and give origin to a spiral septum called the truncoconal septal system, which separates the aorta from the pulmonary artery in such a way that the pulmonary artery emerges from the right ventricle and the aorta arises from the left ventricle (Fig. 6).

With regard to the sigmoid valves' development, as mentioned before, Kramer established an arbitrary divisory line between the truncus arteriosus and the conus at the site of origin of the valves. It is in this area that two endocardial

thickenings appear; both are limited cephalically as well as caudally and are situated between the main truncus ridges. These thickenings do not take part in the partitioning of the truncus but become molded, respectively, into the primordium of the dorsal cusp of the aorta and the ventral cusp of the pulmonary artery; they are called intercalated valve swellings (Fig. 7, *A*,*B*). The expanded margins of the fused ridges of the truncus will form the right and left cusps of both the aorta and the pulmonary artery. The relative position of these cusps will be maintained during the entire length of fetal life.

After birth, and until adulthood, the heart and great vessels rotate in such a manner that the aortic and pulmonary cusps take on a new position. In the aorta the dorsal cusp becomes the right posterior, the right becomes the anterior cusp, and the left is the left posterior cusp of the adult. In the pulmonary artery the ventral cusp turns into the left anterior, the right becomes right anterior, and the left is the posterior cusp of the adult (Fig. 7, *C*,*D*,*E*).

The atrioventricular canal of 4 mm. embryos shows two masses of endocardial cushion tissue situated diametrically opposite, one on the dorsal and the other on the ventral wall. They are the dorsal and the ventral atrioventricular canal cushions. These cushions increase in size and are distinctly seen in embryos of 8 to 9 mm. (Fig. 3,*B*). Each one of these cushions shows a raised elevation at each one of its lateral borders. They are called right and left tubercles of the dorsal and ventral atrioventricular canal cushions.

The dorsal and ventral cushions of the atrioventricular canal fuse and divide this canal into two orifices, one right and one left, in the place where the tricuspid and mitral valves, respectively, will form later.

The following changes are preparatory to the formation of the membranous portion of the interventricular septum: the disappearance of the conoventricular flange accompanied by the displacement of the conus toward the midline, the formation of the truncoconal septum, the fusion of the ventral and dorsal cushions of the atrioventricular canal, and a more advanced development of the ventricles and the primordium of the muscular interventricular septum.

In embryos of 12 to 14 mm. (Fig. 5) which demonstrate the afore-mentioned stage of development, an interventricular communication is observed. This communication is surrounded by the fused cushions of the atrioventricular canal, the thick border of the primordium of the muscular interventricular septum and the conal septum. Such a communication will be closed at the expense of endocardial tissue derived from its borders and will constitute the membranous portion of the interventricular septum. The manner in which these distinct anatomic elements intervene in the closure of said communication is as follows:

The right tubercle of the dorsal cushion of the atrioventricular canal becomes united dorsally with the right side of the thick border of the muscular interventricular septum. The sinistroventral conus ridge also fuses with the right border of the muscular interventricular septum. The dextrodorsal conus ridge swings toward the right orifice of the atrioventricular canal; its medial border fuses with the right tubercle of the ventral cushion of the atrioventricular canal, situated to the right of the thick border of the muscular interventricular septum. This occurs approximately in the same parasagittal plane in which

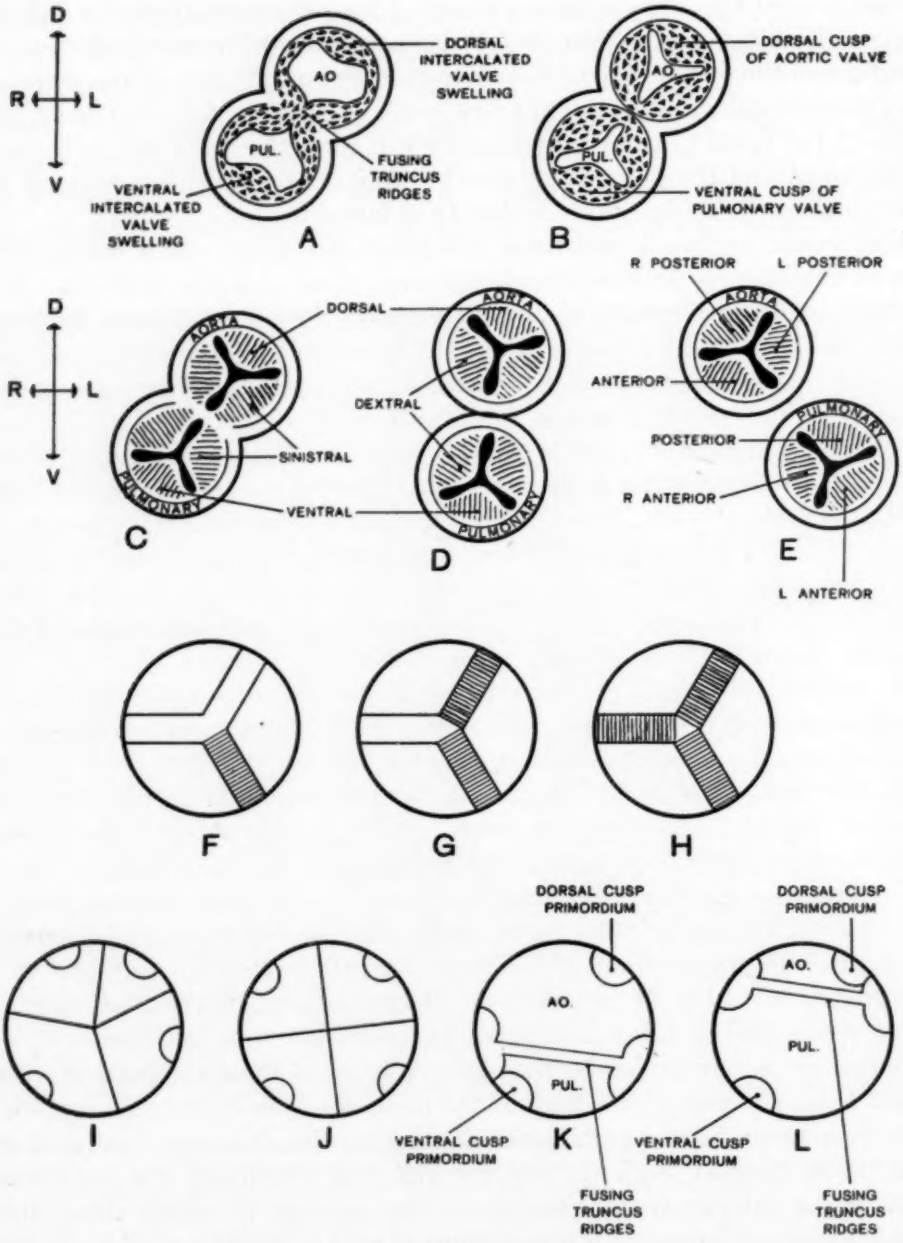

Fig. 7.—*A* and *B*, Schematic drawings to illustrate the origin of the semilunar valves primordia. (Modified from original of Fig. 3C-E, Theodore C. Kramer, Am. J. Anat. **71**:354, 1942.) *C*, *D*, and *E* show the positional relations of the aortic and pulmonary semilunar cusps from the embryonic to the adult condition (I.N.A.). (Modified from original of Fig. 5, Theodore C. Kramer, Am. J. Anat. **71**:357, 1942.) *F*, Bicuspid valve originated by fusion of two adjacent primordial borders. *G*, Splitted cusp by fusion along four adjacent primordial borders. *H*, Monocuspid, funnel-shaped valve formed by partial fusion of all the primordial borders. *I*, A four-cusp valve originated by division of one of the normal primordia. *J*, A four-cusp valve originated by a higher number of primordia. *K*, Bicuspid pulmonary valve. *L*, Bicuspid aortic valve (see text).

the fusion of the sinistroventral conus ridge with the interventricular septum takes place. The lateral border of the dextrodorsal conus ridge fuses with the lateral cushion of the right atrioventricular canal; thus the lateral border of the dextrodorsal conus ridge lies astraddle over the right atrioventricular orifice (Fig. 5).

When these different endocardial elements have united to close the interventricular communication, which occurs in 15 to 17 mm. embryos, the membranous septum is finally formed and thus the separation of the conus of the aorta from the conus of the pulmonary artery takes place. This is the last step in the partitioning of the truncus-conus.

From the embryological data so far analyzed, the following must be especially emphasized:

1. As the partitioning of the truncus arteriosus and conus (bulbus cordis) takes place, there exists only an arbitrary limit between the truncus arteriosus and the conus (bulbus cordis).

2. There is no clockwise or counterclockwise rotation of the truncus-conus. The truncoconal ridges appear, from the beginning, with a clockwise rotation of 180 degrees.

3. No portion of the conus (bulbus cordis) is absorbed in the ventricle. The conus goes into the formation of the cephalic portion of the outflow tracts of both ventricles, and the trabecular zone of the right ventricle.

These facts are not in agreement with Pernkopf and Wirtinger's findings which form the basis of Lev and Saphir's theory[8,9,11,12] for the ontogenetic explanation of truncoconal malformations.

ONTOGENETIC THEORY

We consider truncoconal malformations of the heart as those produced by an abnormal development of the following embryological components, isolated or combined: (1) the conoventricular flange, (2) the truncoconal ridges, and (3) the aortic and pulmonary semilunar primordia.

We must remark that these truncoconal malformations can also occur in combination with other cardiac malformations.

1. *The Conoventricular Flange.*—The truncoconal partitioning normally ends at the stage at which the conus has reached its medial position. A delay in disappearance of the conoventricular flange would impede the normal shifting of the conus toward the midline. This might determine that the partitioning of the truncus-conus would be completed before the conal septum could reach the right border of the muscular interventricular septum. If this were to happen, either both great vessels, pulmonary and aorta, would arise from the right ventricle, or the pulmonary artery would emerge from the right ventricle and the aorta would override in varying degree (an interventricular communication). There would persist therefore Ed. interventricular communication due to the lack of coalescence of the conal septum with the muscular interventricular septum. If, on the contrary, the conoventricular flange disappears too early

and in an exaggerated manner, the conus will shift to the left beyond the midline so that on completion of the truncoconal partitioning, the union between the conal septum and the muscular interventricular septum cannot occur. Thus, we would have the aorta and pulmonary artery arising from the left ventricle or the aorta would leave the left ventricle and the pulmonary artery would override, in varying degree, Ed. interventricular communication. In both cases the lack of alignment of the conal septum with the muscular portion of the interventricular septum, explains the presence of the interventricular communication.

We call *lateral positions* the malformations of the heart due to an abnormal displacement of the truncus-conus in the frontal plane, caused by a defect in the development of the conoventricular flange. They may be divided into dextropositions and sinistropositions. We suggest the term "orthoposition" for the normal (intermedial) position which is a consequence of the normal development of the conoventricular flange.

2. *The Truncoconal Ridges.*—Four types of malformations can occur (alone or combined) as a consequence of an alteration in the normal development of the ridges which constitute the truncoconal septum: (a) complete lack of rotation of the truncoconal septum; (b) incomplete rotation of the truncoconal septum; (c) unequal partitioning of the truncusconus; (d) defects in growth of the truncoconal ridges.

A. *Complete lack of rotation of the truncoconal septum:* If the truncoconal ridges develop without rotation, the truncoconal septum, which is formed from these ridges, will also present no rotation. The pulmonary artery, lying in a sinistrodorsal position at the cephalic (branchial) end of the truncus-conus, will continue in the same position till the caudal (ventricular) end, and the pulmonary artery will arise from the left ventricle. The aorta, on the other hand, which occupies a dextroventral position at the cephalic end of the truncus-conus, will remain in this position till the caudal end, thus arising from the right ventricle in front of the Crista supraventricularis.

In those cases where the truncoconal septum developed without rotation, its caudal end remains at the normal position in relation to the free border of the muscular interventricular septum, and it will fuse with the right side of this septum without the occurrence of an interventricular septal defect. The existence of a ventricular septal defect must therefore be explained by a different mechanism.

The truncoconal malformations arising from a complete lack of rotation of the truncoconal septum will be designated as *transposition* of the large vessels.

B. *Incomplete rotation of the truncoconal septum:* If the truncoconal ridges arise with a rotation markedly below 180 degrees and with a position diametrically opposite, then the truncoconal septum, to which they give rise, will have the same degree of rotation. In this case the caudal (ventricular) end of the truncoconal septum will not be parallel to the free border of the muscular interventricular septum but, on the contrary, will cross over the septum. In this condition both arteries override the septum above an interventricular communi-

cation due to a defect in the coalescence of the conal ridges with the interventricular septum. As a result of a lesser degree the truncoconal septum, the aorta, and the pulmonary artery occupy more or less the same position as the cephalic (branchial) end as at the caudal (ventricular) end. Thus the aorta remains in front of the supraventricular ridge, while the pulmonary artery is located behind the supraventricular ridge.

We call these truncoconal malformations, originating from an incomplete rotation of the truncoconal septum, *partial distortions of the great vessels.* A more complete study of these partial distortions will be the subject of a future publication.

C. *Unequal partitioning of the truncus-conus:* When the truncoconal ridges, origin of the truncoconal septum, are not placed diametrically opposite one another (as it occurs in normal development), we speak of unequal partitioning of the truncus-conus. Thus, if we examine the ridges in the cephalic (branchial) end of the truncus-conus, we find that the imaginary line which would unite these ridges does not correspond to the diameter of this orifice, as normally occurs, but forms a chord. The same prevails at the caudal (ventricular) end of the truncus-conus. If we study the relative position of these chords at both ends, we notice that they occupy a symmetrical position. For example, if the stenotic vessel were to be the pulmonary artery, then we would find that the sinistrodorsal portion of the cephalic (branchial) end of the truncus-conus would be the narrowed one, and that the dextroventral portion of the caudal (ventricular) end, at the conus, would also be of smaller caliber.

The unequal partitioning of the truncus-conus may be at the expense of either the aorta or the pulmonary artery, giving rise to one narrowed and one widened vessel.

When the narrowed vessel is the pulmonary artery, there may be three responsible factors: (1) the sinistroventral truncus ridge emerging more dorsally and the dextrodorsal conus ridge more ventrally (Fig. 8,*A*); (2) the dextrodorsal truncus ridge emerging more dorsally and the sinistroventral conus ridge more ventrally (Fig. 8,*B*); (3) the two ridges of the truncus arise more dorsally and the two conal ridges more ventrally (Fig. 8,*C*).

The reduced caliber of the aorta may be explained by any one of the following three factors: (1) the dextrodorsal truncus ridge comes off more ventrally and the sinistroventral conus ridge more dorsally (Fig. 8,*D*); (2) the sinistroventral truncus ridge emerges more ventrally and the dextrodorsal ridge of the conus more dorsally (Fig. 8,*E*); (3) the two ridges of the truncus arise from a more ventral position and the two conal ridges from a more dorsal one (Fig. 8,*F*).

It is important to emphasize that besides the unequal partitioning occurring with the same degree "of intensity" along the entire length of the truncus-conus, there are the following possibilities: (1) more pronounced degree of stenosis at either the truncus or the conus; (2) the isolated or solitary stenosis of the truncus; (3) the isolated or solitary stenosis of the conus.

An advanced degree of stenosis of the truncus-conus may affect either the pulmonary artery or the aorta. These vessels can be reduced to a fibrous cord.

When the pulmonary artery is the vessel affected the malformation is known as "truncus solitarius aorticus" and in the case of the aorta as "truncus solitarius pulmonalis."

Severe degrees of conal stenosis lead to aplasia of the cephalic part of the outflow tract.

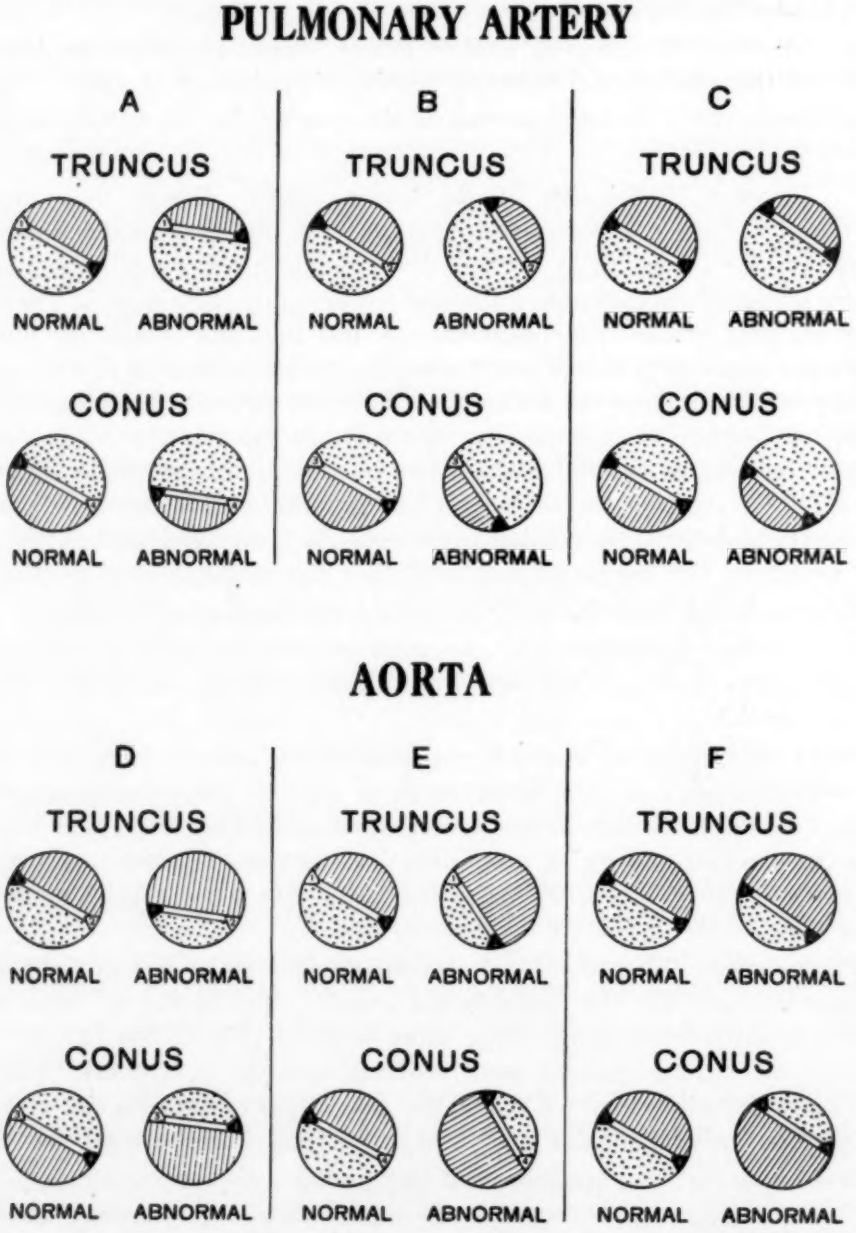

Fig. 8.—Schematic diagrams of the location of the truncus ridge (at the cephalic end) and the conus ridge (at the caudal end), in normal conditions and in cases of unequal partitioning of the truncus-conus. *A*, *B*, and *C*, Unequal partitioning at the expense of the pulmonary artery. *D*, *E*, and *F*, Unequal partitioning at the expense of the aorta. Striped area: pulmonary artery (trunk and conus). Dotted area: aorta (ascending and conus). *1:* Dextrodorsal truncus ridge. *2:* Sinistroventral truncus ridge. *3:* Dextrodorsal conus ridge. *4:* Sinistroventral conus ridge. Areas on black represent the ridge abnormally emerged.

In all those cases in which the stenosis affects the aortic or pulmonary conus without other associated defects, the conal septum will not reach the muscular portion of the interventricular septum and will thus impede the formation of the membranous portion of the interventricular septum. The vessel of a greater diameter will override the interventricular septal defect.

The malformations arising from a lack of equal partitioning of the truncus-conus are called *unequal partitioning at the expense of the pulmonary artery* and *unequal partitioning at the expense of the aorta.*

D. *Defects in growth of the truncoconal ridges:* If the truncoconal ridges fail to develop, we will have a single, or common truncus. This common truncus will override the muscular portion of the interventricular septum, i.e., over an interventricular communication due to the absence of that portion of the membranous interventricular septum, formed by the conal ridges at that level.

The aorticopulmonary septum is incomplete when the truncoconal ridges are only formed at the cephalic end of the truncus-conus. We find a vessel with the characteristics of a common truncus at its caudal end and with only a portion of the pulmonary trunk at its cephalic end from which spring the right and the left pulmonary arteries.

If the arrest in development of the truncoconal ridges occurs only in limited zones, abnormal defects will appear in the truncoconal septum. If they are located in the truncal portion of the truncoconal septum, above the cusps, they will appear as communications between the aorta and the pulmonary trunk. If the defect is located in the conal portion of the truncoconal septum, we will have, anatomically, a high anterior interventricular communication, located below the cusps of that vessel which is located in front of the supraventricular ridge (Crista supraventricularis). This vessel will be the pulmonary artery if the defect is not combined with transposition of the great vessels, and if it is combined there it will be the aorta. This defect, in the left side of the heart, will be situated in the high part of the cephalic portion of the outflow tract of the left ventricle.

These malformations may occur alone or in combination with lateral positions, transposition, unequal partitioning, and valvular defects.

3. *The Aortic and Pulmonary Semilunar Primordia.*—As it was previously discussed in this paper, in the adult heart in situ (I.N.A.) the anterior cusp of the aorta was the right cusp in the embryo; the left posterior cusp was the left cusp, and the right posterior was the dorsal cusp in the embryo. In the pulmonary valve the right anterior cusp of the adult was the right cusp of the embryo; the left anterior was the ventral cusp, and the posterior was the left cusp of the embryo (Fig. 7, *C,D,E*).

The B.N.A. system labels the cusps in accordance with the relative position which they would have in an isolated heart, whose septum is the axis of the right and left positions. This, in fact, represents the position which the cusps have in situ in the embryonal or fetal heart, and will help to identify altered embryonal components (Fig. 7, *C,D*).

The total or partial absence of the primordia of the aortic and pulmonary cusps will produce either an acuspid, monocuspid, or bicuspid valve.

If the total number of cusp primordia is normal, but fusion of two adjacent borders takes place during development, then a bicuspid aortic or pulmonary valve is formed (Fig. 7,*F*); if this fusion takes place along four adjacent primordial borders, then there will be one split cusp (Fig. 7,*G*). When all of the primordial borders become fused in a limited manner, then a monocuspid funnel-shaped valve will result (Fig. 7,H).

If all of the primordial cusps were to fuse along their entire borders we would have a nonperforated membrane referred to as valvular atresia.

When there is a greater number of cusp primordia, or the primordia, normal in number, become divided, a valve formed by varying number of cusps (four, five, six, etc.) is present. These cusps may be normal or hypoplastic (Fig. 7, *I*,*J*).

A deficient development of one or several cusps primordia will give rise to hypoplastic cusps.

All cusp malformations may occur in valvular ostia of normal or diminished caliber. In ostia of diminished caliber there is an additional fusion factor due to displacement of the cusp primordia, especially those primordia which are derived from the truncoconal ridges (Fig. 7, *K*,*L*).

Those valvular defects due to fusion of the cusps may be either congenital or acquired. In these cases the differential diagnosis is, as a rule, possible through histologic study of the cusps raphes. This malformation may also appear isolated or combined with transposition, lateral positions, unequal partitioning, or defects in growth of the truncoconal ridges.

ANATOMIC SYNTHESIS OF CONGENITAL TRUNCOCONAL MALFORMATIONS

An anatomic analysis of the congenital truncoconal malformations occurring alone, or in combination, will be now made in accordance with our theory.

1. *Isolated Lateral Positions.*—The general anatomic characteristics of isolated lateral positions are:

a. Isolated dextropositions. The aorta and the pulmonary artery may emerge from the right ventricle or the pulmonary artery may emerge from the right ventricle and the aorta override, in varying degrees, an interventricular communication (Fig. 9, *A*,*B*).

b. In isolated sinistropositions the two vessels may emerge from the left ventricle or the aorta from the left ventricle and the pulmonary artery overrides, in varying degree, an interventricular communication (Fig. 9, *D*,*E*).

c. In the isolated orthoposition, term reserved for the normal position (intermediate) of the great vessels, the aorta arises from the left ventricle and the pulmonary artery emerges from the right ventricle (Fig. 9,*C*).

All cases of isolated lateral positions are further characterized by normal caliber of the aorta and the pulmonary artery. It is important to emphasize that the pulmonary artery always emerges in front of the supraventricular ridge (Crista supraventricularis).

2. *Isolated Common Truncus.*—The following are the general anatomic characteristics of isolated common truncus: A single vessel leaves the heart and overrides an interventricular communication over approximately equal areas of both ventricles (Fig. 9,*F*).

3. *Isolated Transposition.*—The general anatomic characteristics of isolated transposition are: The aorta emerges from the right ventricle in front of the supraventricular ridge (Crista supraventricularis). The pulmonary artery emerges from the left ventricle. The ascending aorta lies ventral to the pulmonary trunk and runs parallel to it. Both great vessels are of normal caliber (Fig. 9,*G*).

4. *Isolated Partial Distortion.*—These are the general anatomic characteristics of isolated partial distortion: Both the aorta and the pulmonary artery override an interventricular communication. The aorta arises from both ventricles in front of the supraventricular ridge (Crista supraventricularis), and lies ventral and parallel to the pulmonary trunk. The two great vessels are of normal caliber (Fig. 9,*H*).

5. *Isolated Unequal Partitioning at the Expense of the Pulmonary Artery.*—The general anatomic characteristics of isolated unequal partitioning at the expense of the pulmonary artery

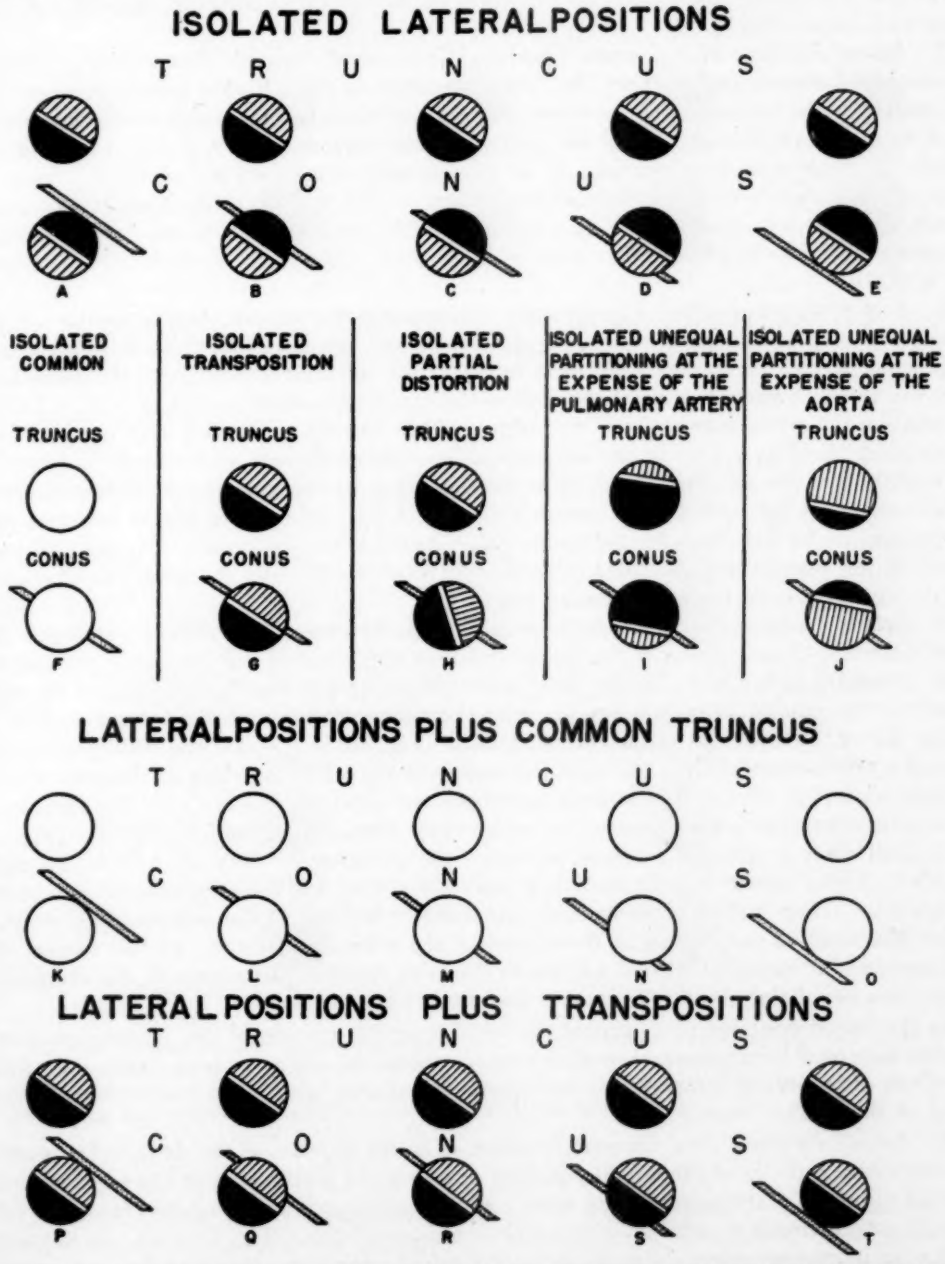

Fig. 9.—Schematic diagrams of the positions of the great vessels at the cephalic end of the truncus and at the caudal end of the conus, as well as the relations of the conal region of both vessels with the interventricular septum. *F*, *K*, *L*, *M*, *N*, and *O* represent the cephalic end of the common truncus, and its caudal end in relation with the interventricular septum. Black area: aorta (ascending and conus). Striped area: pulmonary artery (trunk and conus). Dotted area: interventricular septum.

are: The pulmonary artery arises from the right ventricle in front of the supraventricular ridge (Crista supraventricularis), and shows a stenosis of the cephalic part of the outflow region. The aorta overrides an interventricular communication and is of normal or larger than normal caliber (Fig. 9,*I*).

6. *Isolated Unequal Partitioning at the Expense of the Aorta.*—The general anatomic characteristics of isolated unequal partitioning at the expense of the aorta are: a stenotic aorta emerges from the left ventricle and the pulmonary artery, of normal or larger than normal caliber, overrides an interventricular communication and arises in front of the supraventricular ridge (Crista supraventricularis) (Fig. 9,*J*).

7. *Lateral Positions Plus Common Truncus.*—The general anatomic characteristic of lateral positions plus common truncus are: In the dextropositions the common truncus emerges entirely from the right ventricle or else overrides an interventricular communication with the greatest part of its ostium to the right side of the interventricular septum (Fig. 9, *K,L*). In the orthoposition the common truncus overrides an interventricular communication covering a more or less equal area at both sides of the interventricular septum (Fig. 9,*M*). In the sinistropositions the common truncus emerges completely from the left ventricle or else overrides an interventricular communication, with the greatest part of its orifice to the left side of the interventricular septum (Fig. 9, *N,O*).

8. *Lateral Positions Plus Transposition.*—The general anatomic characteristics of the lateral positions plus transposition are: In dextropositions the aorta and the pulmonary artery emerge from the right ventricle or the aorta emerges from the right ventricle and the pulmonary artery overrides, in variable degrees, an interventricular communication (Fig. 9 *P,Q*). In the orthoposition the aorta emerges from the right ventricle and the pulmonary artery arises from the left ventricle (Fig. 9,*R*). In the sinistropositions the pulmonary artery emerges from the left ventricle and the aorta overrides, in variable degrees, an interventricular communication, or both vessels emerge from the left ventricle (Fig. 9, *S,T*). All cases of lateral positions plus transposition are further characterized by normal caliber of both great vessels; the aorta emerges in front of the supraventricular ridge (Crista supraventricularis), and the ascending aorta lies ventral and runs parallel to the pulmonary trunk.

9. *Lateral Positions Plus Unequal Partitioning at the Expense of the Pulmonary Artery.*—The general anatomic characteristics of the lateral positions with unequal partitioning at the expense of the ulmonary artery are: In the dextropositions both great vessels emerge from the right ventricle or the pulmonary artery emerges from the right ventricle and the aorta overrides, in variable degree, an interventricular communication (Fig. 10, *A,B*). In the orthoposition the pulmonary artery emerges from the right ventricle and the aorta overrides an interventricular communication (Fig. 10,*C*). In the sinistropositions the pulmonary artery and the aorta override an interventricular communication, or both vessels emerge from the left ventricle (Fig. 10, *D,E,*). Still there is another frequent variant: the pulmonary artery may leave the right ventricle by a very narrow cephalic portion of this outflow tract and the aorta may arise from the left ventricle. There will be no ventricular septal defect because of the superimposed sinistroposition plus unequal partitioning at the expense of the pulmonary artery. In this variant the conal portion of truncoconal septum will fall in line with the muscular aspect of the ventricular septum, thus permitting the development of the membranous portion.

In the lateral positions plus unequal partitioning at the expense of the pulmonary artery, the aorta may be of normal or greater than normal caliber, and the pulmonary artery emerges in front of the supraventricular ridge (Crista supraventricularis) with a stenosis of the cephalic portion of this outflow tract.

10. *Lateral Positions Plus Unequal Partitioning at the Expense of the Aorta.*—The general anatomic characteristics of the lateral positions plus unequal partitioning at the expense of the aorta are: In the dextropositions the aorta and the pulmonary artery emerge from the right ventricle or both vessels override an interventricular communication (Fig. 10, *F,G*). In the orthoposition the pulmonary artery overrides an interventricular communication and the aorta emerges from the left ventricle (Fig. 10,*H*). In the sinistropositions the pulmonary artery overrides, in variable degrees, an interventricular communication and the aorta emerges from the left ventricle, or both vessels arise from the left ventricle (Fig. 10, *I,J*). In the lateral positions plus unequal

partitioning at the expense of the aorta, the pulmonary artery emerges in front of the supraventricular ridge (Crista supraventricularis) and is of normal or greater than normal caliber, while the aorta is of smaller caliber than normal.

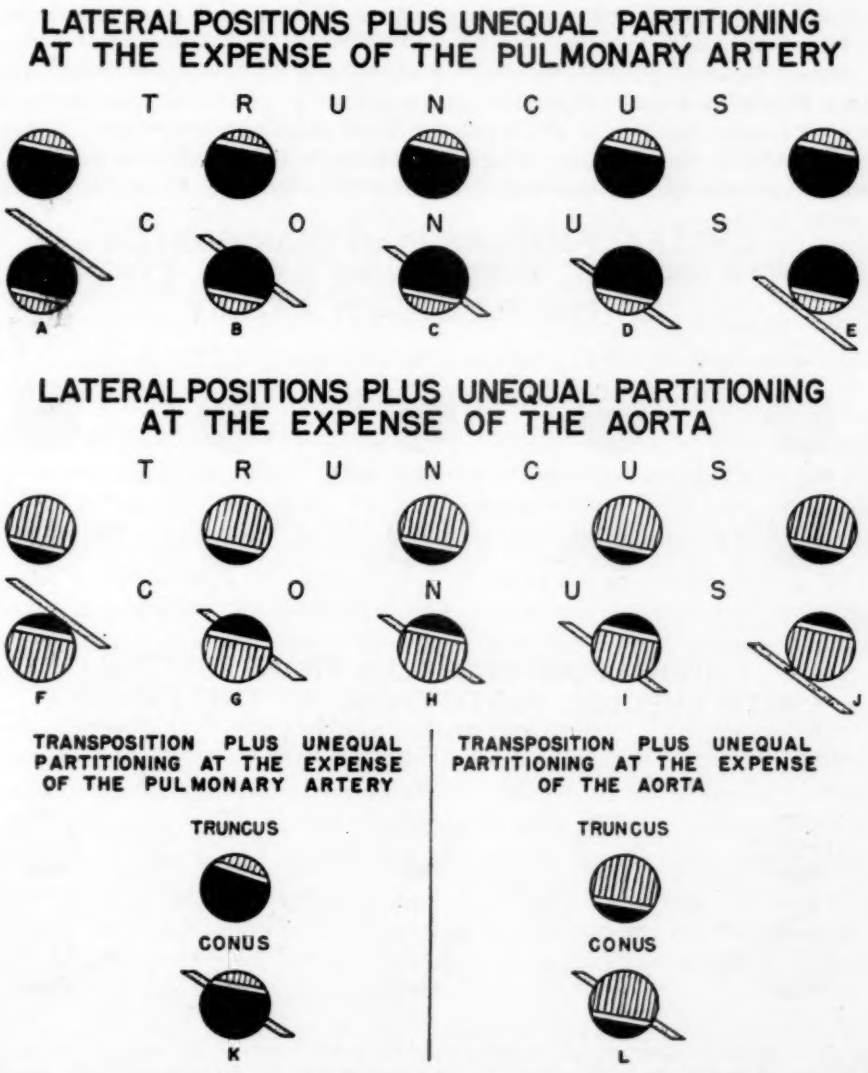

Fig. 10.—Schematic diagrams of the positions of the great vessels at the cephalic end of the truncus and at the caudal end of the conus, as well as the relations of the conal region of both vessels with the interventricular septum. Black area: aorta (ascending and conus). Striped area: pulmonary artery (trunk and conus). Dotted area: interventricular septum.

11. *Transposition Plus Unequal Partitioning at the Expense of the Pulmonary Artery.*—The general anatomic characteristics of transposition plus unequal partitioning at the expense of the pulmonary artery are: A stenotic pulmonary artery emerges from the left ventricle and the aorta, of normal or increased caliber, overrides an interventricular communication. The ascending aorta lies ventral and parallel to the pulmonary trunk. It arises from both ventricles in front of the supraventricular ridge (Crista supraventricularis) (Fig. 10,*K*).

12. *Transposition Plus Unequal Partitioning at the Expense of the Aorta.*—The following are the general anatomic characteristics of transposition plus unequal partitioning at the expense of the aorta: A stenotic aorta (of trunk as well as of conus) emerges from the right ventricle in front of the supraventricular ridge (Crista supraventricularis), and the pulmonary artery is of normal or greater than normal caliber. It overrides an interventricular communication. The ascending aorta is situated ventrally and runs parallel to the pulmonary trunk in its entire length (Fig. 10,*L*).

13. *Lateral Positions Plus Transposition With Unequal Partitioning at the Expense of the Pulmonary Artery.*—The general anatomic characteristics of the lateral positions plus transposition with unequal partitioning at the expense of the pulmonary artery are: In the dextropositions the aorta and the pulmonary artery emerge from the right ventricle or the aorta, and the pulmonary artery overrides an interventricular communication (Fig. 11, *A*,*B*). In the ortho-

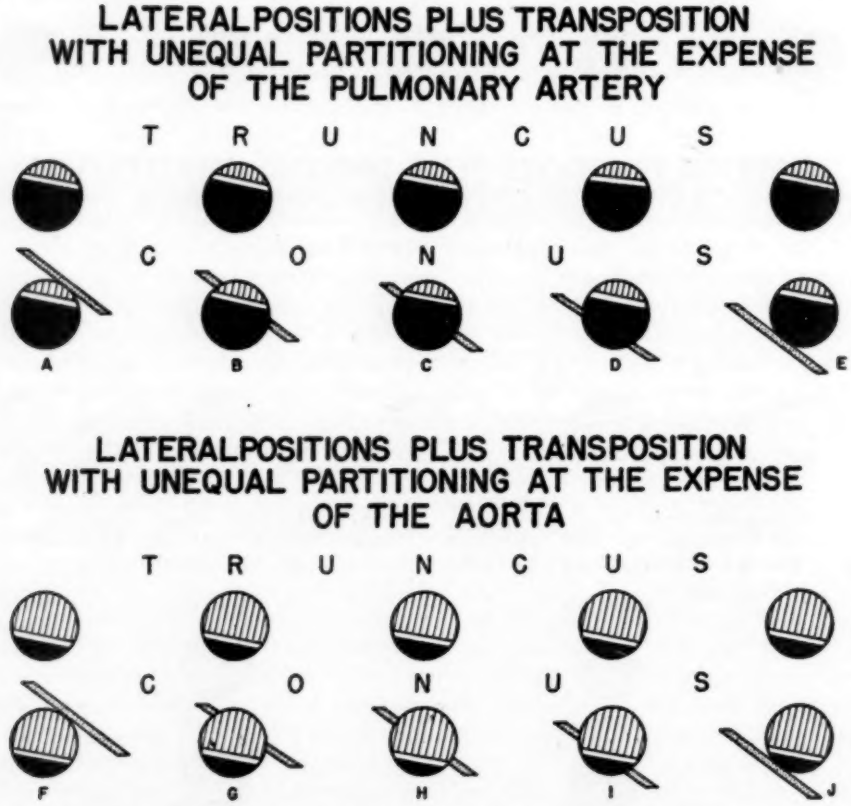

Fig. 11.—Schematic diagrams of the positions of the great vessels at the cephalic end of the truncus and at the caudal end of the conus, as well as the relations of the conal region of both vessels with the interventricular septum. Black area: aorta (ascending and conus). Striped area: pulmonary artery (trunk and conus). Dotted area: interventricular septum.

position the pulmonary artery emerges from the left ventricle and the aorta overrides an interventricular communication (Fig. 11,*C*). In the sinistropositions the pulmonary artery emerges from the left ventricle and the aorta overrides an interventricular communication. Both vessels may emerge from the left ventricle (Fig. 11, *D*,*E*). In the lateral positions plus transposition with unequal partitioning at the expense of the pulmonary artery the aorta emerges in front of the supraventricular ridge (Crista supraventricularis) and the ascending aorta is located ventral and parallel to the pulmonary trunk in its entire length. The pulmonary artery is of smaller caliber than normal, and the aorta is of normal or greater than normal caliber.

14. *Lateral Positions Plus Transposition With Unequal Partitioning at the Expense of the Aorta.*—In the dextropositions both the aorta and the pulmonary artery emerge from the right

ventricle or the aorta emerges from the right ventricle and the pulmonary artery overrides an interventricular communication (Fig. 11, *F,G*). In the orthoposition the aorta emerges from the right ventricle and the pulmonary artery overrides an interventricular communication (Fig. 11,*H*). In the sinistropositions both the pulmonary artery and the aorta override an interventricular communication, or the aorta and the pulmonary artery emerge from the left ventricle (Fig. 11, *I,J*). In the lateral positions plus transposition with unequal partitioning at the expense of the aorta, the pulmonary artery is of normal or greater than normal caliber, and the aorta is of smaller caliber than normal (with subaortic stenosis). The aorta emerges in front of the supraventricular ridge (Crista supraventricularis) and the ascending aorta is located, in its entire length, ventral and parallel to the pulmonary trunk.

Some of the congenital malformations here analyzed have not been found in our material. However, on studying abnormal prematures, fetuses, and embryos, it is possible to observe such type of cardiac malformations, some of them incompatible even with intrauterine life.

APPLICATION OF OUR THEORY TO THE INTERPRETATION OF THE MOST FREQUENT CONGENITAL TRUNCOCONAL MALFORMATIONS

Common Truncus.—The common truncus is due to a lack of development of the truncoconal septum. This malformation may occur alone or in combination with lateral positions. If it occurs alone we will have a single vessel overriding the interventricular septum (see the first group of cases classified by Collet and Edwards[6]). In the second group from the same table the common truncus emerges from the right ventricle: common truncus plus dextroposition; and in the third group it arises from the left ventricle: common truncus plus sinistroposition.

Eisenmenger Complex.—This is a lateral position (dextroposition) which may occur alone or in combination with unequal partitioning at the expense of the aorta. The aorta and the pulmonary artery, of equal caliber, may emerge from the right ventricle or the pulmonary artery may emerge from the right ventricle, and the aorta overrides the septum in variable degrees.[4,6] These cases would be isolated dextropositions of different degrees. It also may occur that, with the great vessels in the position mentioned, the aorta is of smaller caliber than normal.[6,10] These are cases of dextroposition plus unequal partitioning at the expense of the aorta.

When, in young children, a high interventricular communication is located below the aortic cusps and opens into the inflow tract of the right ventricle, at the level of the septal cusp of the tricuspid valve, it is practically impossible to differentiate it from an Eisenmenger complex. This happens because normally (orthoposition) the fusion of the conal septum with the interventricular septum is in the parasagittal plane, giving rise to an aorta slightly deviated to the right of the muscular interventricular septum.

Tetralogy of Fallot.—The tetralogy of Fallot is an unequal partitioning at the expense of the pulmonary artery, which may be isolated or combined with a lateral position (dextroposition). If the stenotic pulmonary artery emerges from the right ventricle and the aorta overrides slightly the interventricular septum,[4] an isolated unequal partitioning at the expense of the pulmonary artery

is present; but if the stenotic pulmonary artery emerges from the right ventricle together with the aorta,[6] the case is that of an unequal partitioning plus dextroposition.

We have found, in our material, that at times there is no relation between the degree of stenosis of the pulmonary artery and the degree of aortic overriding. For example, we have found cases with a very severe stenosis of the pulmonary conus with a slight aortic overriding; such is possibly due to the isolated unequal partitioning. On the other hand, there may be a slight stenosis of the pulmonary artery with a marked overriding of the aorta, which may even make the vessel arise entirely from the right ventricle. This could be attributed to the presence of an important lateral position (dextroposition) superimposed to an unequal partitioning. Summarizing, the pathologic characteristics of the tetralogy of Fallot are:

a. Cases with a severe stenosis of the pulmonary conus and with a slight aortic overriding: probably due to an isolated unequal partitioning at the expense of the pulmonary artery.

b. Cases with a severe stenosis of the pulmonary conus with an accentuated overriding of the aorta: resulting, probably, from an unequal partitioning at the expense of the pulmonary artery plus lateral position (dextroposition). The overriding of the aorta will depend as much upon the unequal partitioning as upon the dextroposition.

c. Cases with a slight pulmonary conal stenosis with the aorta emerging from the right ventricle or severe overriding of the aorta: most probably due to a slight unequal partitioning at the expense of the pulmonary artery plus marked dextroposition.

The unequal partitioning, as it has been explained in accordance with our theory, may affect the trunk as well as the pulmonary conus, or it may affect only the cephalic portion of the outflow tract at various levels. This could or could not be associated with valvular malformations.

Truncus Solitarius Aorticus.—This is an extreme unequal partitioning at the expense of the pulmonary artery and it may occur alone or in combination with lateral positions (dextro- or sinistropositions).

When the aortic truncus emerges overriding the interventricular septum,[4] it may be due only to unequal partitioning. The degree of overriding will depend upon the degree of lateral position. If the truncus solitarius aorticus emerges from the right or left ventricle,[4] there will be unequal partitioning plus a dextro- or sinistroposition, respectively.

Transposition of the Great Vessels.—We use the term "isolated transposition" to designate an anatomic picture characterized by the failure of crossing of the aorta with the pulmonary trunk. The aorta emerges from the right ventricle in front of the supraventricular ridge (Crista supraventricularis) and the pulmonary artery arises from the left ventricle. This is due to the complete lack of rotation of the truncoconal septum. Such a condition corresponds to that designated by Edwards[6] as "complete transposition of the great vessels."

Transposition of the great vessels may be isolated or combined with other malformations: lateral positions, unequal partitioning, etc. One of the cases

of tricuspid atresia (type IIa Table V-4)[6] described by Edwards presents an associated truncoconal malformation. The truncoconal malformation is characterized, anatomically, by the aorta arising in front of the supraventricular ridge (Crista supraventricularis) and overriding an interventricular communication. At the same time there is a stenotic pulmonary artery which emerges from the left ventricle behind the supraventricular ridge (Crista supraventricularis). Both vessels are vertical and parallel. This would be an example of transposition of the great vessels plus unequal partitioning at the expense of the pulmonary artery. We are not certain if the overriding aorta is due solely to unequal partitioning, or if a factor of lateral position is also added because in the description of the case the degree of aortic overriding is not precisely stated.

Specimen number 1067 of the Instituto Nacional de Cardiología of México shows the right and left atria opening into the left ventricle, which, in turn, communicates with the right ventricle through a large opening situated in the membranous portion of the septum. Furthermore, there is a truncoconal malformation consisting of the aorta emerging from the right ventricle in front of the supraventricular ridge (Crista supraventricularis) without crossing the trunk of the pulmonary artery; it runs ventral and parallel to it. The pulmonary artery, with a severe stenosis of the conus and hypoplasia of the trunk, also comes off from the right ventricle behind the supraventricular ridge (Crista supraventricularis). We interpret this case as a transposition of the great vessels plus unequal partitioning at the expense of the pulmonary artery with dextroposition.

Taussig-Bing Complex.—In regard to the Taussig-Bing complex we will have to make a few preliminary remarks due to the existing discrepancy between the original description of Taussig and Bing, and those of Edwards,[6] Lev,[10] and Brown.[1]

The anatomic features, as described by Taussig and Bing[14] are:

a. The aorta leaves entirely from the right ventricle.
b. The pulmonary artery arises primarily from the right ventricle and partially overrides a high interventricular communication.
c. A muscular ridge separates the two great vessels.
d. Right ventricular hypertrophy.
e. The pulmonary artery and its branches are dilated.

In the anatomic description of the specimen it is mentioned that a muscular ridge separates the two great vessels but does not state which vessel lies ventrally. However, in the diagram the pulmonary artery is shown ventral to the aorta and overrides an interventricular communication. The aorta is behind the pulmonary artery and emerges entirely from the right ventricle.

The anatomic data given by Edwards[6] in regard to the Taussig-Bing complex are:

a. The aorta lies in a ventral plane and to the right of the pulmonary trunk; it emerges entirely from the right ventricle.
b. The pulmonary artery emerges primarily from the left ventricle and partially overrides a high ventricular septal defect.

c. The origin of the aorta is separated from that of the pulmonary artery and from the septal defect by a muscular ridge, "probably the crista supraventricularis."
d. Right ventricular hypertrophy.
e. The caliber of the pulmonary artery is greater than normal and greater than that of the aorta.

In the anatomic description he points out that the aorta lies ventrally and to the right of the pulmonary trunk; that it emerges entirely from the right ventricle, and is separated from the origin of the pulmonary artery and from the interventricular communication by the Crista supraventricularis. This leads us to think that the aorta is situated in front of the supraventricular ridge. Edwards' diagram demonstrates clearly our assertion.

Fig. 45 of Brown and Gerlis'[1] atlas corresponds to Edwards' anatomic description of the Taussig-Bing complex, and also to that by Lev.[10]

We shall interpret the Taussig-Bing complex just as described by Edwards, Lev, and Brown, as a transposition plus unequal partitioning at the expense of the aorta with or without dextroposition (this depending upon the degree of pulmonary overriding).

Taussig and Bing's original description cannot be explained through our theory. This may be due to either one of the two following facts: (1) To an error in the description or in the drawing of the figure illustrating the original paper. (2) To the existence of congenital cardiopathies which can only be partially explained by our theory.

SUMMARY

1. A review of the classical concepts about the development and partitioning of the truncus-conus and the formation of the membranous ventricular septum of the human heart is made.

2. An ontogenetic theory is proposed to explain congenital truncoconal malformations. This theory is based upon the work of Davis, Streeter, and Kramer, as well as on the study of pathologic specimens from the Instituto Nacional de Cardiología of México, and from medical literature.

3. Our ontogenetic theory considers truncoconal congenital malformations as a consequence of developmental alterations of the conoventricular flange, the truncoconal ridges, and the primordia of the aortic and pulmonary cusps.

4. Old concepts are re-evaluated and new ones are established in relation to lateral positions, transposition, unequal partitioning at the expense of the aorta or pulmonary artery, common truncus, and valvular defects.

5. Anatomic and embryologic correlations are made in order to permit the pathologic diagnosis of these malformations.

6. The different pictures of isolated and combined trucoconal malformations (which actually exist or may theoretically exist according to the proposed theory) are described.

7. More common congenital truncoconal malformations are interpreted according to this theory: common truncus, Eisenmenger's complex, Fallot's tetralogy, truncus solitarius aorticus, transposition of the great vessels, and the Taussig-Bing complex.

SUMMARIO IN INTERLINGUA

1. Es presentate un revista del conceptos classic in re le disveloppamento e le partition de trunco e cono e in re le formation del membranose septo ventricular del corde human.

2. Es proponite un theoria ontogenetic pro explicar congenite malformationes thrunco-conal. Iste theoria es basate super le labores de Davis, Streeter, e Kramer como etiam super le studio de specimens pathologic ab le Instituto National de Cardiologia de Mexico e ab le litteratura medical.

3. Nostre theoria ontogenetic considera congenite malformationes truncoconal como consequentia de alterationes disveloppamental del collar conoventricular, del crestas trunco-conal, e del primordios del cuspides aortic e pulmonar.

4. Conceptos traditional es re-evalutate e nove conceptos es establite in re positiones lateral, transposition, e partition inequal al expensa de aorta o arteria pulmonar, trunco commun, e defectos valvular.

5. Correlationes anatomic e embryologic es facite pro permitter le diagnose pathologic de iste malformationes.

6. Es describite le differente aspectos de isolate e combinate malformationes trunco-conal (le quales existe de facto o pote exister theoricamente de accordo con le theoria proponite).

7. Le plus commun congenite malformationes trunco-conal es interpretate de accordo con nostre theoria. Le malformationes assi interpretate include trunco commun, complexo de Eisenmenger, tetralogia de Fallot, trunco solitari aortic, transposition del grande vasos, e le complexo de Taussig-Bing.

Professor Demetrio Sodi-Pallares and Dr. Fernando Cisneros were very helpful in the final preparation of this text and its figures. Their constructive criticism and helpful suggestions are very much appreciated and hereby acknowledged.

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Announcement

The Cuban Cardiological Society, through its Congress Committee, has the pleasure of informing you that the V INTERAMERICAN CONGRESS OF CARDIOLOGY, sponsored by the Interamerican Cardiological Society, will be held at Havana, Cuba, Nov. 11 to 17, 1956.

The Congress will include scientific and social activities.

Scientific activities: (1) Plenary sessions: panel discussions, symposia, and lectures; (2) Presentation of scientific papers; (3) Scientific exhibits; (4) Technical exhibits; and (5) Motion pictures program.

The morning hours will be devoted to plenary or general sessions only, and in the afternoon hours there will be simultaneous scientific sessions devoted to presentation of papers. There will be four panel discussions and four symposia, each to be given by five speakers; also, four lectures will be delivered. The names of the speakers will be announced on future directives. The following subjects have been selected for discussions:

Panels: (1) Cerebrovascular accidents; diagnosis and modern treatment; (2) Actual treatment of coronary disease; (3) Modern aspects of arrythmias; (4) Treatment of hypertensive vascular disease.

Symposia: (1) Atherosclerosis: etiology and treatment; (2) Chronic cor pulmonale; (3) Clinical electrocardiography and vectorcardiography; (4) Present status of heart surgery.

Those wishing to present papers must submit abstracts of not more than 200 words before Aug. 1, 1956. According to the regulations of the Interamerican Cardiological Society, all the papers must be previously approved by the local Cardiological Society. If the local societies are nonexistent, the papers should be sent directly to the Secretary-General of the Congress (Apartado 2108, Havana, Cuba), or to the Secretary-General of the Interamerican Cardiological Society (Dr. T. Ortíz Ramírez, Instituto Nacional de Cardiología, Mexico, D. F.). The time allotted to each paper shall be ten minutes and five minutes for discussion. Complete regulations will be given in advance.

Scientific Exhibit.—Invitations to exhibit will be issued only to Institutional groups upon request. Those interested are kindly asked to demand information. The Technical Exhibit will include the latest advances in the therapeutics and instrumental cardiology.

The social activities of the Congress will include the opening reception, official banquet, social and artistic events, and sight-seeing tours.

Postcongressional tours are under consideration by this committee, if sufficient members express their interest in this event in advance.

The registration fee will be $25.00 and will include all social activities and the official banquet. Associate membership (wives and family) has been arranged at a cost of $10.00. Money orders may be sent to the Treasurer, Dr. Luis Ortega Verdes. All mail should be addressed to: V Interamerican Congress of Cardiology, Apartado 2108, Havana, Cuba.